SACHRP Minutes, October 9-10, 2012

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Secretary's Advisory Committee on Human Research Protections (SACHRP)
Tuesday, October 9, 2012 – Wednesday, October 10, 2012
Minutes

Voting SACHRP Members Present:
Barbara Bierer (Chair), Albert J. Allen, Gary L. Chadwick, Carl H. Coleman, Thomas Eissenberg, David G. Forster, Steven Joffe, Susan Krivacic, Suzanne M. Rivera, Lainie Friedman Ross, Stephen O. Sodeke

Tuesday, October 9, 2012

Welcome: Opening Remarks
Barbara Bierer, M.D., SACHRP Chair

Dr. Bierer welcomed attendees to the 29th meeting of SACHRP and reviewed the agenda. She announced that Jeff Botkin, a former SACHRP member, will be the next SACHRP Chair. She welcomed Thomas Eissenberg, who is replacing Gary Gibbon as a SACHRP member. She announced that SACHRP's charter has been renewed by the Secretary of HHS through 2014. The Chair then gave a brief overview of the agenda and expressed the hope that SACHRP would be able to reach consensus on the recommendations to be presented.

The Chair expressed appreciation for the work of Mr. Forster, a departing member, who will continue as Co-Chair for the Subcommittee on Harmonization, and for the many contributions of Dr. Sodeke, whose term is also ending.

The minutes for July 2012 were unanimously approved. Mr. Forster gave the recorder minor changes that did not require discussion.

Dr. Bierer reflected on the accomplishments of SACHRP during her tenure as Chair. She said she was impressed at the amount of work the committee has done.

The Chair observed that the committee's first letter in her term expressed support for additional funding for OHRP; today, however, OHRP's budget is one-third of what it was in 2009.

A selected list of SACHRP accomplishments included:

- With David Strauss's leadership, producing a framework for conducting research on persons with impaired decisionmaking that has proven helpful in framing analysis on research issues;
- Recommending the inclusion of the Office for Civil Rights (OCR) as an ex officio member;
- Initiating a subcommittee on harmonization;
- Producing recommendations on a wide variety of issues, such as financial conflicts of interest, informed consent, IRB membership, component analysis, and investigator education; and
- Offering extended comments on an Advanced Notice of Proposed Rulemaking (NPRM) that may lead to revisions to the Common Rule.

Dr. Bierer highlighted some remaining work, including:

- Addressing the meaning of respect for community;
- Coming to terms with healthcare reform and comparative effectiveness research;
- Addressing incidental and nonincidental results for communities affected by research;
- Considering compensation for research-related injuries; and
- Providing direction for considering ethical questions in international research.

She noted that Common Rule agencies are doing much better job of becoming a single system and addressing sources of confusion in guidance. The Chair observed, however, that process issues have in her view inhibited the committee's work. SACHRP has not been able to discuss compensation for research-related injuries or international research because of OHRP's conflicting sense of priorities. Dr. Bierer and many committee members differ from government in their view that it is helpful to air this type of issue. The fact that OHRP is responsible for the committee's budget and agenda makes it difficult for the committee to fulfill its charge of advising the Secretary on the issues it views as significant.

The individuals who are members of SACHRP and its subcommittees have served tirelessly. Subcommittee members are, in particular, "unsung heros." The Chair also expressed appreciation for the work of Dr. Menikoff, Ms. Gorey, and Ms. Chirinos. She noted there are no simple answers for many of the issues SACHRP considers. She felt she was leaving the responsibility of the Chair in "good hands" with Dr. Botkin.

Report of Issues

Jerry Menikoff, M.D., J.D., Director, Office for Human Research Protections (OHRP)

Dr. Menikoff welcomed everyone. Noting that the success of SACHRP depends on the willingness of people to give their best effort, he commended Mr. Forster for his "amazing mind" and ability to "think outside the box." He also praised Dr. Sodeke for his thoughtfulness and his concern for protecting subjects. Finally, he said that Dr. Bierer has played a "huge" role in SACHRP's recent accomplishments, noting her work went "far beyond what is required."

The Director then welcomed Dr. Eissenberg, noting that his background in psychology is needed to balance concerns related to biomedical research with those pertaining to social science. He also welcomed Dr. Botkin as "one of great leaders in the field of bioethics." He said OHRP was "thrilled" that he has accepted the responsibility of serving as Chair.

Dr. Menikoff reported that OHRP has been busy since SACHRP's last meeting. The Education Division has been reaching an increasing number of people in person and through technology. OHRP and FDA continue to work together to promote harmony in agency policies.

The Director commented that the *Journal of the American Medical Association* (JAMA) gave unprecedented coverage to a study of the use of a hip pad to prevent injury in elderly subjects. The JAMA article expressed concern that some risks of the study were not disclosed to subjects and fully agreed with OHRP's findings and corrective action. Determination letter scan be found on OHRP's website:

http://www.hhs.gov/ohrp/detrm_letrs/YR11/jun11a.pdf
http://www.hhs.gov/ohrp/detrm_letrs/YR12/feb12a.pdf

Dr. Menikoff observed that cases like this one help show what is and is not working in the system and reaffirm the need for vigilance.

Dr. Bierer added to the information provided by Dr. Menikoff. She said that authors of the study had concluded that the hip pads did not prevent injury. Hip Saver, a competitive manufacturer of the same product tested, sued the authors for injury to their business, claiming that people fell preferentially on the side the pad was on and that if this were taken into account it would be clear that the pads are effective. To date, their suit has not been successful; it would be strengthened if the manufacturer could prove that researchers withheld information that would contradict their conclusions. The critical question for SACHRP is what it would mean for the research community if researchers could be sued for conclusions reached in a peer-reviewed publication. The Chair noted that the case involved issues related both to data integrity and to informed consent, as well as First Amendment rights under the U.S. Constitution.

Subpart A Subcommittee (SAS)

David K. Nelson, M.S., CIP, SAS Co-Chair; David Borasky, M.P.H., CIP, SAS Co-Chair

Co-Chairs reviewed the charge of the subcommittee, its membership, meetings to date, and Secretarial letters that incorporate SAS recommendations.

Recommendations on Investigator Responsibilities

See:

- Attachment A. Draft Recommendations Regarding Investigator Responsibilities, as Presented
- Attachment B. Recommendations Regarding Investigator Responsibilities, as Revised

Mr. Nelson and Mr. Borasky reminded SACHRP that the topic of investigators' responsibilities has previously been addressed by SAS, but SACHRP did not approve the recommendations it brought forth at the time. The recent ANRPM issued by OHRP, which signaled its interest in regulatory changes to the Common Rule, makes reconsideration of the topic timely. At SACHRP's previous meeting (July 10-11, 2012), SAS presented recommendations. SACHRP asked SAS to consider its input on the recommendations and return with revised recommendations.

The following changes were made in the draft document:

- A citation to relevant FDA regulations was added.
- In the third paragraph, wording was added to link the proposed regulatory changes to the goal of creating a stronger "culture of responsibility" among investigators.
- In §46.104, the committee moved items related to delegating tasks and ensuring that study staff and trainees are appropriately trained and qualified closer together, since they are closely related.
- SACHRP removed a reference to the limitations of IRBs in monitoring research as unnecessary.
- Various members offered changes in wording to improve readability and clarity.

Action. After making the changes in wording discussed above, SACHRP unanimously approved the revised recommendations.

Research Findings and Duration of Involvement. On the second day of the meeting, following a public comment asking SACHRP to address the issue of findings that should be provided to subjects, SACHRP approved the addition of the following language:

- *Investigators are responsible for providing subjects with significant new findings developed during the course of the research that may relate to their willingness to continue participation, in accordance with §46.116 and as approved by the IRB.*

SACHRP also added language specifying that investigators should communicate to subjects "the expected duration of the subject's participation."

Recommendations on Informed Consent and Waiver of Consent

See:

- Attachment C. Draft Recommendations Regarding Informed Consent and Waiver of Consent, as Presented
- Attachment D. Recommendations Regarding Informed Consent and Waiver of Consent, as Revised

Co-Chairs explained that SAS's goals were to re-examine and clarify the elements of consent (especially the distribution among required and optional elements and the documentation of IRB determinations) and to clarify the criteria for waiver of consent. They pointed out that the current construct of the Common Rule leads to variable understanding and application of informed consent requirements. Consent forms are unduly long and complex, and IRBs fail to exercise the flexibility allowed by regulation. Many also have difficulty applying the criteria for a waiver of consent. Proposed reforms, as explored in the NPRM of July 2011, have opened the door to rethinking current requirements and revisiting prior SACHRP recommendations that did not foresee the possibility of new regulations. They explained that the draft presented at the meeting incorporates changes agreed on at the previous SACHRP meeting (July 10-11, 2012).

Introductory material (paragraphs 1-6). SACHRP revised the following statement:

> *…IRBs have variable understanding of when waivers of selected elements of consent are appropriate. As a result, IRBs have frequently required investigators to include information in consent documents that adds little value to the consent process, for example, a statement that "the only alternative is not to participate in this research."*

Members agreed that such statements often have no value at all, so they modified "little value" to "little or no value." They also qualified the statement to indicate that "many" IRBs do this, while others do not. Finally, they felt that variable understanding of the requirement may exist, but variable understanding of requirements is not the "underlying issue." The revised passage now reads:

> *In practice, the regulations governing waivers of informed consent at §46.116(d) are constructed in such a way that **many** IRBs require investigators to include information in*

*consent documents that adds little **or no** value to the consent process. An example is a statement that "the only alternative is not to participate in this research."*

SACHRP also changed a reference to study "methodology" to the more precise "research methods." Members observed that the proposal did not "consolidate" elements of informed consent, but rather "reorganized" them. Finally, they included a reference to the need to harmonize new regulatory language with FDA.

General requirements for informed consent: introduction and "basic" elements. In reference to a description of "procedures" as a required element, SACHRP members agreed that informed consent documents often include descriptions of procedures that are unrelated to the research, including "standard of care" procedures. SACHRP revised language to refer to "research-related activities" instead of "procedures." They decided to avoid reference to both "standard of care" and "procedures" because they are associated primarily with biomedical research.

Dr. Chadwick noted that the Common Rule references the need to inform subjects of "reasonably foreseeable" risks, while FDA regulations refer to "probable" risks. Mr. Coleman observed that existing Common Rule language implies that anything the investigator foresees should be reported, regardless of how rare it is. Instead, he thought the researcher should be disclosing what a reasonable subject would want to know. The Chair held that "rare but significant" risks should be disclosed. Dr. Chadwick reminded SACHRP that informed consent forms often contain 20 pages of risks, and there is a need to narrow down what is presented to those risks that might reasonably affect the subject's decision. SACHRP agreed on the following wording for information to be provided:

A description of those foreseeable risks or discomforts about which a reasonable potential subject would want to know due to the probability or seriousness of their occurrence.

SACHRP also agreed to add a statement indicating, "If there are no direct benefits to subjects this should be stated." Finally, SACHRP included in this section an assurance that "refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled."

General requirements for informed consent: "optional" elements. Dr. Joffe said the word "optional" to describe this list of elements was misleading, since in some cases they are appropriate and would be required. SACHRP decided to remove the reference to "basic" and "optional" elements of consent, replacing the subtitle with a narrative introduction to each list.

Members discussed whether or not a reference to compensation for research-related injuries should be included. While compensation is seldom offered, Dr. Joffe said failure to indicate that there is no mechanism for providing compensation could be an "invitation to a lawsuit." SACHRP agreed that subjects should be informed of whether or not compensation and payment for medical treatment are to be provided and added a reference in section (3).

Dr. Joffe questioned the need to refer to the possible effects of treatment on the fetus or embryo (section 4). Dr. Chadwick explained the reference was intended to address the "unknown unknowns" that could pose risks to the research participant. SACHRP decided to make the reference open-ended, agreeing to say that the IRB might require "a statement that the research may involve risks that are currently unforeseeable."

Ms. Krivacic stressed that it is important for subjects to know how long the research will last. The committee added "the expected duration of the subject's participation" as another element that may be "material."

A SACHRP member asked why subjects needed to consent to being told about "significant new findings." Dr. Joffe suggested that this should be included because it created a sense of obligation to communicate with subjects if findings emerge. Dr. Allen agreed, noting that new knowledge might emerge from the trial itself. Mr. Nelson commented, however, that in the case of a survey, participants would probably not be informed of new research. The statement remained, with the understanding that the IRB will determine whether or not it is material to a particular study.

A SACHRP member wondered why a subject would want to know how many subjects are included in the protocol. Noting that this information was to be included only when "material," the reference was retained as potentially relevant in some instances.

Waiving informed consent. Dr. Allen questioned whether speed should ever be the primary justification for a waiver. He observed that existing wording (d[4]) simply suggests it should not be sole consideration, leaving open this possibility. Mr. Coleman also questioned whether cost was an appropriate consideration. Dr. Cates stressed that the IRB must have "permission to say no" when the investigator is complaining about the cost or inconvenience associated with the consent process.

Members agreed that convenience, cost, and speed might all be appropriate considerations provided that they do not compromise either ethics or the quality of the science. The committee replaced the original wording – "the waiver or alteration of consent should not be justified solely on the basis of convenience, cost or speed" – with the following:

> *Once the IRB has determined that the waiver or alteration does not adversely impact the ethical nature or scientific rigor of the research, logistical issues (e.g., cost, convenience, and speed) may be considered.*

SACHRP also removed a reference to research being "reasonable in relation to the benefits of the research" as unclear and unnecessary.

In reference to requests for a waiver that include a request for identifiers, Dr. Menikoff stressed that it should be a "rare scenario" in which investigators are given access to identifiers. Dr. Joffe differed, saying it would not necessarily be rare but would have to be justified on the basis of science, ethics, and the approach to ensuring confidentiality. He said the guidance is intended to indicate what should be considered as IRBs determine what materials could be shared. Dr. Bierer pointed out that the recommended guidance states that the investigator should receive "the minimum necessary information to accomplish the research." Mr. Forster suggested that items (1) and (2) be combined, making clear that access to sensitive materials could be granted only for minimal risk research. SACHRP agreed, resulting in a final document with only two key considerations.

Action. SACHRP unanimously approved the recommendations as revised.

Remarks and Swearing in of New Member

Howard K. Koh, M.D., M.P.H., Assistant Secretary for Health (ASH)

Dr. Koh expressed his appreciation for SACHRP's work and his respect for the quality of people advising the Department, as well as his appreciation for Dr. Menikoff's guidance on the important issues addressed by the committee.

He thanked the outgoing Chair, Dr. Bierer, for her "perseverance and patience in this chapter of public health history." He said she had been a "wonderful leader" who "left a legacy." He also said he was "thrilled" that Dr. Bodkin, a talented man with "tremendous expertise," will be the new Chair.

The ASH expressed appreciation to Mr. Forster, who has provided leadership to address issues related to people who are decisionally impaired as research subjects and harmonization of regulations. He also expressed gratitude to Dr. Sodeke for his "passionate commitment to human subject protections." Finally, he welcomed Dr. Eissenberg, a "highly qualified" new member. He then swore in Dr. Eissenberg as a Special Government Employee.

Legal Status of E-Signatures

Laura Odwazny, JD., Senior Attorney, Public Health Division, Office of General Counsel

Note: PowerPoints for all presentations are posted on the OHRP Web site. Please see these resources for more detailed information.

Ms. Odwazny stated that OHRP will allow an electronic signature to be used to document informed consent and does not require any specific method for signatures, so long as they are "legally valid within the jurisdiction where the research is to be conducted." Because the investigator and subjects may not be in the same jurisdiction, the question arises as to whether the pertinent laws are those in place where the researcher is located or where the subjects are located. Currently, OHRP allows IRBs and regulated entities to determine on their own which should apply. FDA's guidance also does not specify which jurisdiction or jurisdictions are relevant. One possibility for guidance from OHRP would be to state in the FAQ that:

- An e-signature that met requirements of jurisdiction of the researcher would satisfy the 46.117 documentation requirement, or
- An e-signature that met requirements of jurisdiction of the researcher *and* the subjects would satisfy the 46.117 documentation requirement.

Another key issue is whether or not the investigator knows the location of the research subjects. If the investigator has this knowledge, it could be argued that he or she should assess the legal framework that applies in each jurisdiction.

The speaker suggested that one pertinent analogy is to telemedicine. Several medical malpractice cases have occurred in which the question arose as to where a person must be located to bring forward a lawsuit. The legal precedent is that the practice of medicine is understood to be occurring both in the state where the physician is located and in the state where the patient is located.

Discussion

Dr. Bierer noted that determination of relevant jurisdictions also applies to research on the Internet. She did not favor providing specific guidance; instead, she suggested that it would be helpful for OHRP to make it clear that OHRP will not comment further on this subject. Mr. Forster agreed that IRBs would like to know they have the latitude to make this decision.

Dr. Allen, however, saw the need for an expanded FAQ that would "walk people through the issues." Dr. Chadwick thought it would be useful to say what is needed to satisfy the requirements of §46.111. He emphasized that the least helpful course of action would be to require research to comply with legal requirements in *both* the researcher's and subjects' jurisdictions. Ms. Odwazny observed that most IRBs appear to be looking at applicable laws in the researcher's jurisdiction. Dr. Chadwick recalled that many committee members have spoken in favor of funding a data base that holds data on research-related laws in each state, saving hundreds of IRBs the resources required to do the same research on their own.

The Chair asked how requirements for electronic signatures would vary for adult as opposed to child subjects. Ms. Odwazny said there could be some unique considerations for children. SACHRP members wondered whether it would be a concern if the subject's state states a different legal age for when children should be considered adults. Especially in regard to research using the Internet, it is not clear to what lengths the researcher is expected to go to determine whether subjects are children or adults. Mr. Forster said that services are available that provide background checks; however, they are costly. Dr. Ross said that there are many psychosocial studies for which she would not want a 13-year-old to become a subject.

A SACHRP member pointed out that the Children's Online Privacy Act (COPA) has specific requirements that are pertinent to research (see http://www.ftc.gov/ogc/coppa1.htm). Sometimes researchers are aware of these requirements but are less knowledgeable about the implications of the Common Rule when research may involve children.

Informed Consent Issues in Cluster-Randomized Trials

Andrew McRae, M.D., Ph.D., University of Calgary

Note: PowerPoints for all presentations are posted on the OHRP Web site. Please see these resources for more detailed information.

Dr. McRae told SACHRP that cluster-randomized trials (CRTs) are rapidly becoming a gold standard research methodology in health services, education, social science research, and fields involving program evaluation. CRTs randomize social groups such as nursing homes or villages in order to get larger sample sizes, test group-level interventions such as methods of malaria control, avoid experimental contamination, study individual and group effects, and simplify study logistics.

Dr. McRae cited three examples of CRTs (see PowerPoints for additional study details and references):

- A community intervention trial for smoking cessation designed to evaluate the effect of a multi-modal, community-level smoking cessation intervention. The randomized clusters were 22 communities in the U.S. and Canada.
- A study of computerized decision-support in primary care designed to evaluate the use of a computerized system to support evidence based clinical decision-making for the management of asthma and angina in adults. The randomized clusters were 60 general practices in England.
- A study of antiseptic cleansing of the umbilical cord to prevent neonatal morbidity and mortality in Nepal that was designed to evaluate the effectiveness of topical application of chlorhexidine to the umbilical cord to prevent infection and death. Randomized clusters included 413 communities in Nepal.

Ethical issues that arise in this type of research include:

- Who is a research subject?
- When, and from whom, is consent required?
- Harm-benefit issues, e.g., does clinical equipoise apply to CRTs?
- Are there group-level interests?

The speaker reviewed recommendations from the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials:
http://crtethics.wikispaces.com/file/view/Ethics+in+CRTs+Draft+consensus+statement+Feb+2012.pdf

The Ottawa statement defines a research subject is an individual whose interests may be affected as a result of study interventions or data collection procedures. The individual may be:

- the recipient of an experimental (or control) intervention, or
- the direct target of an experimental (or control) manipulation of his/her environment.

The subject may be someone with whom an investigator interacts for the purpose of collecting data about that individual, or it could be someone about whom an investigator obtains identifiable private information. Professionals who are used in the intervention (e.g., doctors) are also considered research subjects. Dr. McRae said he would like to raise awareness in the research community that "there may be more subjects than they think." To be considered a subject by virtue of environmental manipulation, the environmental change must be designed to affect target individuals and must affect their interests.

Dr. Allen observed that in some traditional clinical trials, clusters may be created without intending to do so. He gave the example of a study in which a child is randomized to a drug or placebo and the researcher wants to collect data from the child's school for comparison. Dr. McRae would not consider the schools to be clusters in this case but agreed that some similar issues could arise.

Dr. McRae held that consent is not required for people included in a cluster who do not meet the definitional criteria for being considered subjects. He noted that getting consent is often prohibitively difficult in large clusters (for example, a study regarding the effects of adding fluoride to drinking water in cities). Also, if subjects knew to which intervention their community had been randomized,

the validity of the results might be compromised. For example, some might decide they would rather receive the intervention another community is getting. In some cases, if the intervention is one to which the community will be exposed regardless of what subjects might say, the consent process may be meaningless. The Ottowa Statement recommends that:

- Researchers must obtain informed consent from human research subjects in a cluster randomized trial, unless a waiver of consent is granted by a research ethics committee under specific circumstances.
- When subjects' informed consent is required, but recruitment of subjects is not possible prior to randomization of clusters, researchers must seek subjects' consent for trial participation as soon as possible after cluster randomization.
- A research ethics committee may approve a waiver or alteration of consent requirements when
    - the research is not feasible without a waiver or alteration of consent, **and**
    - the study interventions and data collection procedures pose no more than minimal risk.

Discussion

Ethical approaches to informed consent. Dr. Chadwick observed that consultations with the community seem especially important in this type of research. Dr. McRae responded that many such studies do engage community stakeholders. Community leaders sometimes speak for their communities. The speaker added that although community-level interventions are always appropriate for cluster randomized trials, it is possible to do individual-level interventions as cluster trials to avoid contamination. He stressed that individual randomized trials were easier to do, especially from a statistical perspective, and researchers would select this option if they could.

Concerned that subjects might not be receiving information pertinent to sound decisions about personal health, Dr. Menikoff asked what subjects were told in the study of antiseptic cleansing of the umbilical cord. Dr. McRae said the alternative to the cluster that received antiseptic treatment was a "dry cord," which was the community standard of care for the communities. Subjects could opt out of either arm, but the intervention with antiseptic was not available other than through the study. Dr. Menikoff noted that researchers would still be obligated, from a regulatory perspective, to tell subjects about the possible benefit of antiseptic use. The information they received about antiseptics might well be useful. He did not see the experimental arms as described as representing "clinical equipoise," nor did he view the study as minimal risk research. He said the study as described could not be done in the U.S. as government-funded research. Dr. McRae confirmed that such studies are often done in developing countries for logistical reasons.

Dr. Joffe commented that there were two reasons researchers might wish to discuss the "other" arms of an intervention. One would be that the subject has options he or she might wish to pursue in the event the subject declines to participate. Another would be to help the subject understand the purpose of the study. A SACHRP member commented that it was important to offer subjects as much "decisional liberty" as possible.

Quality Improvement and CRT. A SACHRP member asked the speaker where he would draw the line between quality improvement efforts and CRTs. The speaker replied that he would not try to do so and did not see the distinction as germane.

Caregivers as subjects. The Chair commented that it was appropriate to define health care providers as subjects when they are asked to participate in CRTs. Another speaker observed, however, that the providers might lose their jobs or face professional discipline as a result of actions they take as subjects. This is a risk IRBs need to consider.

Next Steps. A SACHRP member suggested that SACHRP might wish to develop a guidance document on how to conduct CRTs within the U.S. regulatory framework. The Chair agreed. She noted that the current health care system is "dependent on this methodology" and usually uses it without informed consent. She felt it was appropriate to study the subject. However, no specific action steps were identified at the meeting.

Public Comment

Mr. James McNerney of Kaiser Permanente asked SACHRP to return to unresolved issues related to investigator responsibilities. These were addressed on the second day of the meeting, resulting in additional changes to the approved recommendations from SAS.

Wednesday, October 10, 2012

Subcommittee on Harmonization (SOH)

David Mr. Forster, J.D., SOH Co-Chair

The Co-Chair reviewed membership, meetings to date, and completed activities. The latter include recommendations regarding HHS Conflict of Interest Policies, recommendations on the NPRM on HITECH, the definition of a nonscientist, the addition of FDA considerations to SAS FAQs on biospecimens, the definition of a minor change in research, and early processes in research.

IRB Knowledge of Local Context

See:

- Attachment E. SACHRP Recommendation on IRB Knowledge of Local Context with Respect to Increasing Use of Single IRB Review, as Presented
- Attachment F. SACHRP Recommendations on Consideration of Local Context with Respect to Increasing Use of Single IRB Review, as Revised

SOH prepared recommendations regarding IRB Knowledge of Local Context. At the previous SACHRP meeting (July 10-11, 2012), SACHRP heard a presentation by Dr. Pritchard of OHRP focusing on local context, and SOH presented initial comments on local context for discussion. The document presented incorporates SACHRP feedback from the previous meeting.

Introduction. SACHRP revised the document to consistently use the word "recommends" when a recommendation was offered and bolded each recommendation to facilitate tracking.

SACHRP removed a reference to biomedical research as unnecessary; the issue of how to address local context can be relevant to any category of research.

Dr. Ross questioned whether the use of single IRBs really reduces administrative burden. Dr. Cates agreed, noting that benefits depend on the type of model used and the study requirements. The statement in the fifth paragraph that "the use of single IRBs can improve quality in many ways, and not just reduce administrative burden…" was revised to read, "the use of single IRBs may improve quality and reduce administrative burden…."

A SACHRP member asked the meaning of the suggestion that OHRP issue guidance harmonized with that of FDA "by the most practical means." A member responded that SOH was concerned that guidance might not be forthcoming for years, and because it is badly needed it should be issued as expeditiously as possible.

Dr. Joffe proposed that the statement, "it is not effective for guidance to recommend specific administrative measures," be revised to clarify SACHRP's recommendation to OHRP. The statement now reads, "SACHRP suggests that the guidance avoid recommending specific administrative measures."

Applicable Laws and Local Standards. A SACHRP member suggested deleting the quotation from the regulations that references "applicable law," but another member countered that without the quotation it would be more difficult to trace the recommendations back to the regulatory requirement they address. Others agreed and the reference was retained.

Mr. Coleman said the reference to "public state law" was not the correct wording. What SACHRP is requesting is a database containing state laws relevant to human subject protection. The new wording was accepted.

An ex officio member questioned the feasibility of developing such a data base. Others countered that IRBs currently are expected to know and apply state laws and currently must conduct the necessary research individually. One member described this as a "colossal waste of effort." Dr. Cates stressed the importance of interpreting laws as well as simply collecting them. She also was not convinced that the work described could be done at a central level. She suggested including a means for consultation regarding interpretation. Dr. Joffe opined that the cost of consultation might be prohibitive. A SACHRP member suggested that a university or private organization might be suited to do the work. Members agreed that it should be left to HHS to determine the best mechanism for addressing the need described.

Members agreed that they needed to clarify the recommendation and to include a reference to maintenance. The original statement read as follows: "It would be valuable to IRBs to have access to a public state law data base. SACHRP encourages the development of such a data base." The revised statement reads:

> *It is critical for IRBs to have access to a compendium of state law relevant to human subject research. SACHRP recommends that the Secretary of HHS support the development and maintenance of such a compendium and other resources to support single IRB review.*

Knowledge of Institutional Policies and Capacity. Language was revised to highlight the recommendation.

Investigator and Study Staff Capability. Dr. Chadwick said the proposed language gives the impression that the IRB has all the responsibility in this area; rather, it is the investigator who is responsible for ensuring staff are credentialed and trained. He agreed that the IRB should consider data such as the number of staff, studies underway, and available equipment; however, the issue is the level of detail required. The original statement was: "The IRB should either assess investigators and study staff itself, or rely upon alternative measures such as an institutional credentialing/privileging process." It was revised to read: "The IRB should also assess relevant information about prior research, noncompliance, criminal activities, state board issues, etc."

Community and Subject Considerations. A SACHRP member pointed out that the recommendations address the reviewing IRB but not the relying IRB. They do not address the need for cooperation and trust or concerns about accountability. Others suggested, however, that the focus is on review and the issues described do not come up under this heading. SACHRP agreed not to add another section to the recommendations.

Action. SACHRP unanimously approved the revised recommendations.

Commentary on OHRP and FDA Draft Guidance Documents on Transfer of Research to New Institutions

See:

- Attachment G. SACHRP Comments on OHRP and FDA Draft Guidance Documents Regarding IRB Transfers, As Presented
- Attachment H. SACHRP Comments on OHRP and FDA Draft Guidance Documents Regarding IRB Transfers, As Revised

Discussion. SACHRP revised the second paragraph to explain why the draft guidance documents are helpful, noting that they "will help to provide consistency and quality to this practice."

Dr. Chadwick questioned whether the term "unified joint guidance" was sufficiently clear. Dr. Menikoff responded that OHRP understood the recommendation as worded.

Dr. Chadwick suggested that the statement that a plan for transfer be "documented" be revised to say instead that it should be "established." Others agreed.

Dr. Joffe asked for clarification of the seventh point, regarding the need to consider local law. Mr. Forster explained that when records are shifted, laws may address the transfer of health data or other concerns. The Chair noted that institutional policies should also be considered. SACHRP agreed to eliminate this point, noting that the following point addresses this concern.

A reference to institutional policy was added in the eighth point (now the seventh) as one of the concerns to be taken into account when data and documents are transferred to a new entity.

Action. SACHRP unanimously approved the revised recommendations.

NeuroNext IRB Experience

Pearl O'Rourke, M.D., Director of Human Research Affairs for Partners HealthCare; Louise Ritz, M.S.B., Clinical Research Program Manager, NIH/NINDS/Office of Clinical Research

Note: PowerPoints for all presentations are posted on the OHRP Web site. Please see these resources for more detailed information.

Remarks by Louise Ritz: NINDS' NeuroNEXT -- The Central IRB Experience

Ms. Ritz explained that the infrastructure for the Network for Excellence in Neuroscience Clinical Trials (NeuroNext) is designed to move Phase II clinical trials along more quickly. NIH's National Institute of Neurological Disorders and Stroke (NINDS) concluded that meaningful interventions could be better targeted if there were an infrastructure that addressed all the relevant diseases. Specific goals were to accomplish the following:

- Test promising therapeutics in Phase 2 Clinical Trials,
- Accelerate drug development through an established clinical trials infrastructure,
- Decrease the time/cost between trial design and trial completion through the use of a central IRB and standing master trial agreements, and
- Coordinate public/private sector efforts.

Following a competitive process to identify a contractor, funding for the project began in September 2011. A total of 25 academic centers are participating. Ms. Ritz observed that NINDS' experience suggested that with a proactive Coordinating Center and central IRB, Reliance Agreements can be executed across wide range of institutions in a range of 1 to 27 days (the median is 20 days). However, a consortium may have multiple FWAs, each of which requires a separate agreement. It is still too early to tell whether the central IRB will meet the objective of saving time. The speaker stressed that the model is designed for a specific network using a cooperative agreement and may not be exportable.

For more information, see: www.ninds.nih.gov/NeuroNEXT or www.neuronext.org

Remarks by Pearl O'Rourke: The NeuroNEXT Central IRB Model

Dr. O'Rourke said that key components of the NeuroNEXT model include

- A Clinical Coordinating Center,
- A dedicated CIRB-CCC liaison person,
- A Data Coordinating Center,
- A research pharmacy,
- Education and site monitoring,
- Robust SOPs, and
- NINDS staff support.

The goals of the CIRB include the following:

- To work collaboratively with local sites,

- To maximize communication and opportunity for input from local sites,
- To provide high-quality, efficient review for multiple sites, and
- To streamline continuing review, amendments, and compliance reporting.

The model was informed by the approach to protocol review used by the Department of Veterans Affairs (VA). The site where the Principal Investigator (PI) is located submits a "parent" protocol for review by the Central IRB (CIRB). The Chair does an initial assessment to see if it is ready for IRB review. If it is, it is sent to all the sites that have indicated interest in the protocol. Sites have 2 weeks to review the protocol and conference calls with the PI to answer any questions. The sites identify any implementation problems, and the CIRB takes these into account when they review the "parent" protocol. Once the parent protocol has been approved, it is sent to the sites, and they then determine whether or not they wish to participate in the protocol as finalized.

Challenges for relying sites include determining how to handle institutional review, provide for ongoing institutional oversight of the research, ensure research compliance with the CIRB, and fulfill responsibilities for its Human Research Protection Program. Sites handled Reliance Agreements in a variety of ways.

Experience to date yields several lessons learned. Dr. O'Rourke said that others seeking to use a similar approach should not underestimate the start-up and long-term costs of Central IRB infrastructure, the confusion resulting from institution-specific assignation of Institutional Responsibility and IRB review responsibility, or the critical role played by trust and familiarity between institutions when developing and negotiating IRB reliance relationships. The network also faced the challenge of working with institutions that include several entities, each of which had its own FWA and required its own Reliance Agreement. Dr. O'Rourke said she would welcome guidance from OHRP clarifying how to handle complex sites that have multiple subcomponents, each with their own FWA. The speaker noted that the NeuroNEXT infrastructure may not be generalizable to multi-site studies that do not have the infrastructure that is provided in the NeuroNEXT model. .

To date, one protocol has been approved. Several grants are in the pipeline. It is too early to determine any metrics regarding review times.

Discussion

Dr. Menikoff thanked the speakers. He commented that he envisions a time when every institution will create internal procedures that will allow it to participate in a network like this one. He suggested that NIH consider helping sites create forms, templates, guidelines, and other resources to facilitate similar networks. The Director requested a copy of the NeuroNEXT Reliance Agreement, which has since been provided. See "CIRB Reliance Agreement Template" and "Master Clinical Trial Agreement at: http://www.neuronext.org/researchers

Dr. O'Rourke commented that the IRB review is easier than "everything else." The many unfunded mandates that institutions have taken on add to the difficulties.

Dr. Bierer commented that Harvard's experience has been that while investigators love this approach, IRB administrators are less enthusiastic. Administration and communication are difficult because of the different information technology systems involved. She stressed that the review process must be linked to a variety of other organizational systems, such as conflict of interest reviews and grants and

contracts, across institutional lines. Dr. Botkin agreed that the time required to address this type of issue has been underestimated.

Dr. O'Rourke clarified that although there are 25 member sites, these 25 sites include more than 60 distinct research sites. As noted above, a reliance agreement was required for every site that had its own FWA. The NeuroNEXT Executive Committee offers each protocol to all of the member sites for consideration, and each site then decides if they have the appropriate patient population and expertise for the particular protocol. Information on how the sites perceive their experience to date has not been collected. However, a conference is planned that will allow them to share their perceptions.

A SACHRP member asked Dr. O'Rourke to clarify how the Conflict of Interest determination is handled. She explained that sites provide a report. If there is a disclosure of conflict of interest, the NeuroNEXT COI committee requests details. Such issues may be specific to a site or may potentially affect all states. If the IRB felt the issue needed to be disclosed to all sites, this could occur. However, the network has not yet encountered a case of Conflict of Interest. Dr. Bierer asked who makes the decision of whether a Conflict of Interest is significant. Dr. O'Rourke said the Standard Operating Procedures do address the issue in detail.

Dr. Chadwick belongs to a network in upstate New York that took two years of setup time. So far there is only one protocol. He noted that it is not worth doing this amount of work unless there are enough protocols to process through the network to make it worthwhile.

Dr. Joffe said that the model may be a "share" or "nonshare" model depending on how the role of IRB staff is defined. Dr. O'Rourke said the model extends only to IRB review. She added that before review begins, the coordinator sends out a feasibility questionnaire, which is completed with input from the PI. Only IRBs that are interested in participating in a particular protocol engage in the protocol review process.

Dr. Allen commented that sponsors and investigators spend a great deal of time coordinating minor changes on protocols for multi-site studies. He thought networks like this would be beneficial.

An FDA ex officio asked how the role of the FDA was handled in the first protocol reviewed by the network, which involved the use of a device. Speakers explained that the PI "worked that through" before the network began its review.

Dr. Cates expressed excitement that the VA model is working for NeuroNEXT. This begins to disprove those who have viewed the VA network as something that would only work for VA.

Speakers clarified that when a "child site" is added, this is accomplished through expedited review.

Investigators from NeuroNEXT member institutions are able to submit a protocol to the NeuroNEXT for consideration. However, all NeuroNEXT research must be reviewed and approved by the CIRB – even for nonmember sites.

A member asked how Master Clinical Trial agreements with industry are handled. Dr. O'Rourke explained that industry approaches NINDs with a concept. Funding is transferred to NINDs, which in turn conveys it to the coordinating center to distribute to participating sites. Industry does not contract with sites individually. There is no line item in the budget to support CIRB activities; rather, the

network pays for the infrastructure and industry pays for the use of that infrastructure. Dr. Allen suggested that companies that are unable to build an infrastructure on their own are more likely to choose to work with an existing one.

Internet Research

Elizabeth Buchanan, Ph.D., Director of the Center for Applied Studies, University of Wisconsin-Stout; Dean R. Gallant, A.B., Assistant Dean for Research Policy and Administration, Harvard University

See:

- Attachment I. Considerations and Recommendations Concerning Internet Research and Human Subjects Research Regulations, With Revisions

Dr. Buchanan and Mr. Gallant presented draft recommendations regarding Internet research, which incorporated suggestions offered by SACHRP at its previous meeting (July 10-11, 2012). SACHRP members provided further input on the document as follows.

Overarching Changes

All recommendations will be bolded in order to make it easier to track them.

Introduction

Dr. Allen suggested that the introduction should state that the ethical principles that apply to all research (e.g., beneficence to persons) apply to Internet research. The following statement was added:

> ***Fundamental Principles***
>
> ***Investigators and IRBs should remember that the Belmont Report's fundamental principles of respect for persons, beneficence, and justice are as applicable to Internet research as they are to any other form of human subjects research. Regardless of how the regulations may be interpreted in individual studies, adherence to these fundamental principles is important to encouraging public trust in the ethical conduct of Internet research.***

Forms and Examples of Internet Research

References related to FDA guidance, including any statements relevant to m-research or apps, may be added later.

Authors deleted a reference to "on-ground counterparts," which was perceived as unnecessary jargon.

The word "paramount," used in reference to investigator responsibilities for "good data stewardship, and heightened awareness of subjects' privacy, confidentiality, and identities," was replaced by "critical." The change was made because the meaning was not "most important" but simply "important."

A SACHRP member suggested recapping the history of this document in the final paragraph of this section.

Regulatory Recommendations

Q1. What is "research involving human subjects" on the Internet? A SACHRP member asked that the statement that "avatars…can be considered human subjects" be revised to clarify that the individual, not the avatar, is the subject. Members agreed that they should be called "virtual representations of human subjects." Investigators should determine whether the avatar is a proxy for the individual and whether the individual's protected health information (PHI) is being collected by the researcher.

Dr. Joffe noted that data must be recorded, not simply accessed, to constitute research. The word "obtained" was considered appropriate.

Q2. What is nonexempt research involving human subjects on the Internet? A SACHRP member suggested that since the question asks "What is nonexempt research…" the first sentence should begin by addressing nonexempt rather than exempt research. In response, the question was changed to: "What is ***exempt*** research."

An ex officio representative of the Department of Defense (DoD) gave the example of nonexempt research involving telemedicine in which the entire intervention is done through Second Life. Examples of nonexempt research were deleted on the grounds that the reader would be familiar with them already.

Q3. When, if ever, is information available via the Internet "private information," and when can subjects "reasonably expect" their private information will not be made public? Dr. Joffe observed that even when information is accessible, it is necessary to consider whether or not the individual might have considered it private. Dr. Bierer commented that virtually any information a person posts might be considered accessible. Dr. Joffe rejoined that some information is accessible only to group members, and some sites say that only group members are invited to post. Mr. Coleman said that it might be easy or hard to become a group member. In either case, he held that unless an individual must prove his or her identity, a site should be considered a public space. Dr. Bierer suggested that the requirement that an individual use a password to be admitted to a site indicates an expectation of privacy.

Dr. Rivera noted that the standard at issue is an ethical rather than a legal one. Even in the common example of a public park as a public space, a person would not consider it ethical to move close to an individual in order to eavesdrop on a conversation. A private conversation can occur in a public space. Consequently, norms should be considered. Analysis involves subjective interpretation of where a situation lies on a spectrum of possibilities. A SACHRP member added that teenagers conceive of privacy differently; culturally determined meanings should be considered in understanding expectations.

Members agreed that researchers should pay close attention to the Terms of Service posted for any site. If it says that research or the use of site data is prohibited, the research should not precede. User license agreements should also be referenced. One member said the subjects' expectations of privacy may not matter; these agreements should determine whether or not the material should be considered private. Dr. Rivera suggested that this is analogous to established procedures for IRB review of research within a site such as a grocery store. The IRB would ask about the grocery store's stated policies regarding

interviews of their customers. Ms. Krivacic asked about situations in which a site has a stated policy but may be sold to a different site with another policy. Members stated that the current terms of service would still govern; future terms are not foreseeable.

Two paragraphs that address nuances were deleted on the grounds that they made the guidance offered less clear.

Ms. Heide, a representative of the HHS Office for Civil Rights, observed that Internet research may involve a number of issues related to the Health Insurance Portability and Accountability Act (HIPAA). A researcher within a HIPAA-covered entity who collects individually identifiable health information and uses it for research purposes may be using protected information, regardless of whether the information is otherwise publicly available or whether collection of the information is allowable under the site's Terms of Service. She agreed to draft a statement for inclusion in the document.

Mr. Coleman suggested adding a statement about why this question is important.

Q4.What is identifiable private information on the Internet? Mr. Coleman suggested that some of the information presented in Question 4 is more relevant to Question 3. After discussion, the questions originally contained in Question 4 were moved to Question 3. SACHRP members did not want to confuse the issue of identifiability with what should be considered public.

Mr. Coleman also suggested that OHRP guidance on biospecimens be deleted as unhelpful.

Dr. Rivera said the guidance should be clearer in regard to when investigators are allowed to determine for themselves that the subject's identity cannot be "readily ascertained" and there is no need for a pre-existing agreement not to try to break the code. Dr. Menikoff said there is a distinction between situations in which there is a third-party agreement not to ascertain individuals' identity and one in which there is no third party and the investigator agrees not to do so.

Ms. Heide observed that the HIPAA Privacy Rule may also relevant and should be referenced in this section. She agreed to provide language for inclusion. The new language will be placed at the end of the material moved to Question 3:

> *In addition to Common Rule considerations, there are implications under the HIPAA Privacy Rule. When a HIPAA-covered entity collects individually identifiable health information and then wants to use or disclose the information for research purposes, the Privacy Rule sets conditions on how covered entities may use or disclose protected health information for research purposes (such as requiring the individual's authorization or a waiver of authorization by an IRB) and requires that the information be safeguarded. Note also that the Common Rule and Privacy Rule have different definitions of identifiability, so information that is not considered identifiable under the Common Rule may be identifiable for Privacy Rule purposes.*

Dr. Menikoff pointed out that the answer to Question 4 does not address cases in which identifiers are stripped. Authors agreed to address this aspect of exemption requirements. He noted that even though people have a clear expectation of privacy in regard to their medical records, the Common Rule says this information can be used if stripped of identifiers. Dr. Ross raised the issue of group harms that can

occur regardless of whether data are stripped, as in the case of the Havasupai (discussed at SACHRP in July of 2010).

Dr. Allen commented that the data often does not exist to determine for certain whether or not a subject has an expectation of privacy, but the subject's expectation remains an important concern from an ethical point of view. Dr. Rivera suggested that the person's expectations should be considered when they are apparent to the researcher, even if the use of information is not contrary to explicit Terms of Service. However, the presumption should be that the information they post can be considered public unless the Terms of Service say otherwise. Dr. Bierer noted that many young people do not expect information they post to be considered private. Another SACHRP member commented that a subject's expectation of privacy is not always reasonable; a conditional sentence stating that the subject's expectation "may not always be reasonable" was changed to "is not always reasonable."

Dr. Joffe said there should not be a special distinction for health-related sites, and a sentence to the contrary was deleted.

Q5. What is intervention or interaction with a subject in research on the Internet? No changes were suggested.

Q6. What are the characteristics of purely public sites? A SACHRP member suggested moving this question closer to Questions 3 and 4, since its content is closely related to them. Dr. Joffe suggested giving examples that help in less straightforward situations. An example might be a discussion forum that is easily accessible and has no published terms of service, but in which participants share personal information that might be considered private.

Q7.What is observation of public behavior online? A member pointed out that the site does not mention the importance of research being consistent with the terms of service for the site on which research is conducted. Dr. Bierer suggested stating the requirement that research should be consistent with Terms of Service early in the document and making clear that it applies throughout rather than repeating it in its section.

Dr. Rivera drafted the following language:

> *To the degree that Terms of Service or explicit prohibitions would preclude the use of data on the internet for purposes of research, the determination that such data should be considered private is more clear. In addition, investigators should note expressed norms or requests in a virtual space which, although technically perhaps not binding, still should be taken into consideration. When in doubt about whether to consider information public or private, investigators are encouraged to consult with their IRB about the specific circumstances. For example [followed by more ambiguous cases].*

Mr. Forster thought expressed norms was too limiting. However, Dr. Rivera said it is not possible to intuit norms that are not expressed.

This material was added to Question 3 prior to the identification of considerations in determining whether or not there is an expectation of privacy when this expectation is not articulated in the Terms of Service.

Q8. Is online education normal educational practice? Mr. Forster suggested that the guidance state more clearly that the answer is "yes, it often is."

Q9.When is information recorded in identifiable manner? Dr. Chadwick suggested that additional information was needed to address the question that was asked directly, rather than starting the answer with a question. New language was added.

Q10. When are data, documents, or records publicly available on the Internet? The second bullet under "publicly available may mean…" was deleted because it was considered redundant with the first bullet.

The original draft concluded with the following sentence: "Investigators and IRBs should ensure that data represented as 'publicly available' are, indeed, available without restriction." Dr. Chadwick commented that there could be a restriction that does not affect public availability, such as the requirement to pay for information. The sentence was amended to specify "…without restriction ***that would limit the proposed use.***"

Members agreed to avoid the use of the term "data use agreement," which would denote HIPAA requirements.

Q11. How do investigators obtain the informed consent/parental permission/assent of subjects for research on the Internet? No changes were suggested.

Q12. When may investigators seek to waive or alter the informed consent of subjects in research on the Internet? The reference to FDA-regulated research was deleted because the FDA ex officio representative said that FDA does not have a comparable waiver.

Q13. How do investigators document the informed consent of subjects for research on the Internet? No changes were suggested.

Q14. Can an electronic signature be used to document consent or parental permission? SACHRP asked that the OHRP FAQ on this subject be identified as the source of this information in the body of the text rather than in a footnote.

Q15. Are investigators required to confirm the real identities of subjects of their Internet research? No changes were suggested.

Q16. What are the relevant concerns for the knowledge of the local research context, i.e., where research "occurs," during the conduct of online research? This question was deleted because guidance on this subject has been archived. New guidance can be cited when and if it is given.

Q17. How does legal jurisdiction apply in Internet research? No changes were suggested.

Q18.What is minimal risk in Internet research? The term "data use agreements" was revised to the more general term, "use agreements." The qualification "widespread" was removed since the regulatory definition in question precedes any use of the Internet, not widespread use.

The ex officio for the Department of Defense observed that "exempt" research is not risk indexed. The reference to this research category was removed.

Q19. How may investigators minimize risk of harm when using sensitive online data? No changes were suggested.

Q20.What forms of online recruitment are used and what is reviewable by an IRB? A SACHRP member suggested listing some research recruitment sites as examples. The term "onground forms" was considered to be jargon and was replaced with "other."

Q21.How is deception conducted in Internet research? A reference to "biasing" subjects' responses was revised to "affecting" subjects' responses.

Action

After discussion, members agreed that they needed time to review the revised document and were not prepared to approve it at this meeting. The revised document will be reviewed at the next SACHRP meeting.

Attachment A. Draft Recommendations Regarding Investigator Responsibilities, as Presented

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research, unlike FDA regulations, does not directly address the roles and responsibilities of investigators involved in research involving human subjects. While IRBs serve a critical function, they are removed from the day-to-day research activities and thus their ability to monitor research activities is limited. Investigators are in the best position to protect participants.

In the recent report "MORAL SCIENCE: Protecting Participants in Human Subjects Research," the Presidential Commission for the Study of Bioethical Issues recommended that "The Common Rule should be revised to include a section directly addressing the responsibilities of investigators. Doing so would bring it into harmony with the Food and Drug Administration regulations for clinical research and international standards that make the obligations of individual researchers more explicit, and contribute to building a stronger culture of responsibility among investigators." We agree that encouraging a culture of responsibility among investigators is an important goal of human subject protection regulations.

SACHRP proposes the addition to 45 CFR 46 of three sections that would cover, at a minimum: (1) responsibilities of investigators; (2) qualification standards for investigators (e.g., training); and (3) investigator documentation/records.

New regulations to ensure investigator accountability would codify the current ethical expectations for investigators who conduct research involving human subjects. Regulations addressing investigator responsibility should emphasize the critical role of the investigator and hold the investigator directly accountable for his/her actions.

Adding investigator responsibilities to the HHS regulations would harmonize HHS regulations with those of the FDA and international standards, uniting the regulatory expectations. Models for delineating investigator responsibilities can be found in the drug and device regulations of the FDA (i.e., Subpart D, 21 CFR Part 312 and Subpart E, 21 CFR Part 812) and in internationally accepted guidelines such as the ICH standards (Good Clinical Practice E-6, Section 4) and the CIOMS International Ethical Guidelines For Biomedical Research.

Therefore, SACHRP recommends the following language for inclusion in 45 CFR 46:

§46.102 (to be added to definitions)

Investigator means any individual responsible for the conduct of research involving human subjects, either for the study as a whole or for an individual site. If the research is conducted by a team at a study site, the investigator is the responsible leader of the team. The responsible person may also be called the principal investigator.

§46.104 Responsibilities of Investigators.

(a) As appropriate to their role in the research, investigators are responsible for ensuring that research is conducted according to:
  (1) sound research design and scientific methods;
  (2) the IRB approved study plan (protocol);
  (3) the terms of the grant, contract and/or signed funding agreements that are applicable to the investigator;
  (4) applicable laws and regulations, including those for protecting the rights, safety, and welfare of human subjects.

(b) When responsibilities are delegated to members of the research team those members shall execute their delegated responsibilities appropriately.

(c) Investigators are responsible for ensuring that members of the research team are appropriately qualified, trained and supervised.

(d) Unless exempt from review, investigators are responsible for obtaining initial IRB approval, prior approval for any modifications to the research and, as required, continuing review of the research.

(e) Investigators are responsible for providing the IRB with sufficient information and materials to make the required determinations in §46.111.

(f) Unless waived by the IRB, investigators are responsible for ensuring that informed consent is obtained in accordance with §46.116 and as approved by the IRB.

(g) Unless waived by the IRB, investigators are responsible for ensuring consent is documented to the extent required by §46.117 and as approved by the IRB.

(h) Investigators are responsible for providing a copy of the informed consent to each subject, unless the requirement of a written consent document is not part of the IRB approval.

(i) When vulnerable populations are involved in research, investigators are responsible for implementing any additional safeguards as required by the IRB.

(j) Investigators are required to permit and facilitate monitoring and auditing, at reasonable times, by the IRB of record, funding entities, sponsors, the Secretary, and other federal and state regulatory agencies, as appropriate.

(k) Investigators shall ensure prompt reporting to the IRB of any noncompliance with the approved protocol or requirements of the IRB, and unanticipated problems involving risks to subjects or others.

(l) Investigators are responsible for personally conducting or supervising the research.

(m) Investigators are responsible for ensuring that study staff and trainees are appropriately qualified and trained.

(n) Investigators are responsible for complying with regulatory and institutional requirements including those relating to financial interests that are relevant to the research.

§46.105 Qualification Standards for Investigators.

(a) As appropriate to their role in the research, investigators must be sufficiently qualified by education, training, and experience to assume responsibility for the proper conduct of the research.
(b) Investigators must assure that they have sufficient time and resources to properly conduct or supervise the research for which they are responsible.

§46.106 Investigator Records, Reports and Documentation.
(a) Investigators are responsible for the safe and secure storage of research data (whether in paper or electronic formats) and for adequately protecting the confidentiality of the data.
(b) Investigators are responsible for the accuracy and completeness of study data.
(c) Investigators must maintain records appropriate to the research (e.g., the study plan, consent forms, and correspondence from the IRB) and permit inspection of the research records in accordance with §46.104(j).
(d) Investigators must maintain records for at least three years after the research ends or for the length of time specified in applicable regulations or applicable institutional or sponsor requirements, whichever is longer, and should take measures to prevent accidental or premature destruction of these documents.
(e) Investigators must submit written reports to the IRB as required by the IRB.

Attachment B. Recommendations Regarding Investigator Responsibilities, as Revised

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

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The HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research, unlike FDA regulations **(312 and 812),** does not directly address the roles and responsibilities of investigators involved in **human subjects** research ~~involving human subjects. While IRBs serve a critical function, they are removed from the day-to-day research activities and thus their ability to monitor research activities is limited.~~ Investigators are in the best position to protect participants.

In the recent report "MORAL SCIENCE: Protecting Participants in Human Subjects Research," the Presidential Commission for the Study of Bioethical Issues recommended that "The Common Rule should be revised to include a section directly addressing the responsibilities of investigators. Doing so would bring it into harmony with the Food and Drug Administration regulations for clinical research and international standards that make the obligations of individual researchers more explicit, and contribute to building a stronger culture of responsibility among investigators." We agree that encouraging a culture of responsibility among investigators is an important goal of human subject protection regulations **and the addition of investigator responsibilities to the regulations would be an important step in fostering this culture.**

SACHRP proposes the addition to 45 CFR 46 of three sections that would cover, at a minimum: (1) responsibilities of investigators; (2) qualification standards for investigators (e.g., training); and (3) investigator documentation/records.

New regulations to ensure investigator accountability would codify the current ethical expectations for investigators who conduct research involving human subjects. Regulations addressing investigator responsibility should emphasize the critical role of the investigator and hold the investigator directly accountable for his/her actions.

Adding investigator responsibilities to the HHS regulations would harmonize HHS regulations with those of the FDA and international standards, uniting the regulatory expectations. Models for delineating investigator responsibilities can be found in the drug and device regulations of the FDA (i.e., Subpart D, 21 CFR Part 312 and Subpart E, 21 CFR Part 812) and in internationally accepted guidelines such as the ICH standards (Good Clinical Practice E-6, Section 4) and the CIOMS International Ethical Guidelines For Biomedical Research.

Therefore, SACHRP recommends the following language for inclusion in 45 CFR 46:

§46.102 (to be added to definitions)

Investigator means any individual responsible for the conduct of research involving human subjects, either for the study as a whole or for an individual site. If the research is conducted by a team at a study site, the investigator is the responsible leader of the team. The responsible person may also be called the principal investigator.

§46.104 Responsibilities of Investigators.

(a) As appropriate to their role in the research, investigators are responsible for ensuring that research is conducted according to:

(1) sound research design and ***~~scientific~~*** *methods;*

(2) the IRB approved study plan (protocol);

(3) the ***applicable*** *terms of the grant, contract and/or signed funding agreements ~~that are applicable to the investigator;~~*

(4) applicable laws and regulations, including those for protecting the rights, safety, and welfare of human subjects.

(b) Investigators are responsible for ensuring that members of the research team, including study staff and trainees, are appropriately qualified, trained and supervised *~~When responsibilities are delegated to members of the research team those members shall execute their delegated responsibilities appropriately.~~*

~~(b) Investigators are responsible for ensuring that members of the research team are appropriately qualified, trained and supervised.~~

(c) Unless exempt from review, investigators are responsible for obtaining initial IRB approval, prior approval for any modifications to the research and, as required, continuing review of the research.

(d) Investigators are responsible for providing the IRB with sufficient information and materials to make the required determinations in §46.111.

(e) Unless waived by the IRB, investigators are responsible for ensuring that informed consent is obtained in accordance with §46.116 and as approved by the IRB.

(f) Unless waived by the IRB, investigators are responsible for ensuring consent is documented to the extent required by §46.117 and as approved by the IRB.

(g) Investigators are responsible for providing a copy of the informed consent document to each subject, unless the requirement of a written consent document is not part of the IRB approval.

(h) ***Investigators are responsible for providing subjects with significant new findings developed during the course of the research that may relate to their willingness to continue participation, in accordance with §46.116.***

(i) When vulnerable populations are involved in research, investigators are responsible for implementing any additional safeguards as required by the IRB.

(j) Investigators are required to permit and facilitate monitoring and auditing, at reasonable times, by the IRB of record, funding entities, sponsors, the Secretary, and other federal and state regulatory agencies, as appropriate.

(k) Investigators shall ensure prompt reporting to the IRB of any noncompliance with the approved protocol or requirements of the IRB, and unanticipated problems involving risks to subjects or others.

(l) Investigators are responsible for personally conducting or supervising the research.

~~(m) Investigators are responsible for ensuring that study staff and trainees are appropriately qualified and trained.~~

(m) Investigators are responsible for complying with regulatory and institutional requirements, including those relating to financial interests, that are relevant to the research.

§46.105 Qualification Standards for Investigators.

(a) As appropriate to their role in the research, investigators must be sufficiently qualified by education, training, and experience to assume responsibility for the proper conduct of the research.

(b) Investigators must assure that they have sufficient time and resources to properly conduct or supervise the research for which they are responsible.

§46.106 Investigator Records, Reports and Documentation.

(a) Investigators are responsible for the safe and secure storage of research data (whether in paper or electronic formats) and for ~~adequately~~ protecting the confidentiality of the data ***in accordance with the approved protocol.***

(b) Investigators are responsible for the accuracy and completeness of study data.

(c) Investigators must maintain records appropriate to the research (e.g., the study plan, consent forms, and correspondence from the IRB) and permit inspection of the research records in accordance with §46.104(j).

(d) Investigators must maintain records for at least three years after the research ends or for the length of time specified in applicable regulations or applicable institutional or sponsor requirements, whichever is longer, and should take measures to prevent accidental or premature destruction of these documents.

(e) Investigators must submit written reports to the IRB as required by the IRB.

Attachment C. Draft Recommendations Regarding Informed Consent and Waiver of Consent, as Presented

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The informed consent requirements found in HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research provide a bedrock protection for individuals participating in research studies. While the regulatory default for non-exempt research is to obtain and document the informed consent of all participants, the regulations anticipated scenarios where this default requirement would be inappropriate given the proposed methodology, the context in which the research would be conducted or the subject population. The regulations included provisions allowing IRBs to waive some or all elements of informed consent when specific conditions have been met.

In practice, the regulations governing waivers of informed consent at §46.116(d) are constructed in such a way that IRBs have variable understanding of when waivers of selected elements of consent are appropriate. As a result, IRBs have frequently required investigators to include information in consent documents that adds little value to the consent process, for example, a statement that "the only alternative is not to participate in this research." In fact, by adding length to consent documents and including irrelevant information it could be argued that the effectiveness of the consent process is diminished. In addition, IRBs struggle to interpret whether and how the criteria should be applied in order to grant a full waiver of informed consent.

SACHRP proposes modification of 45 CFR Part 46.116 in order to: (1) consolidate the elements of informed consent at §116 (a) and (b) into one comprehensive list of elements; (2) empower IRBs to waive selected elements of consent when deemed appropriate by the IRB; and (3) clarify the circumstances in which an IRB may grant a complete waiver of informed consent.

The proposed restructuring of 45 CFR Part 46.116 would not erode the ethical foundation embodied in informed consent. Modification of the regulations would instead permit IRBs to more consistently grant partial or complete waivers of informed consent without impinging on the ethical validity of the consent process or the research itself. These waivers are already permitted in the existing regulations, but nuances in the language have deterred IRBs from exercising the flexibility that the regulations were intended to provide.

Therefore, SACHRP recommends the following new language for inclusion in 45 CFR 46:

§46.116 General requirements for informed consent.

Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

(a) Basic elements of informed consent. Except as provided in paragraph (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:

(1) A statement that the study involves research, an explanation of the purposes of the research, a description of procedures that subjects will be asked to undergo with emphasis on those procedures that are directly relevant to a decision to participate, and identification of any procedures that are experimental;
(2) A description of any reasonably foreseeable risks or discomforts to the subject;
(3) A description of any benefits to the subject or to others which may reasonably be expected from the research;
(4) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights; and
(5) A statement that participation is voluntary, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(b) Optional elements of informed consent. When appropriate, one or more of the following elements of information may also be provided to each subject. In the event an optional element is not to be included, it is not necessary to determine or document that the waiver criteria under paragraph (c) or (d) of this section are met:

(1) A disclosure of appropriate alternative procedures or courses of treatment, that might be advantageous to the subject;
(2) A statement describing the extent to which confidentiality of records identifying the subject will be maintained;
(3) A statement of whether medical treatment is available if injury occurs, where further information may be obtained, and whom to contact in the event of a research-related injury to the subject.
(4) A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable;
(5) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
(6) Any additional costs to the subject that may result from participation in the research;
(7) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(8) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject; and
(9) The approximate number of subjects involved in the study.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the basic elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designated to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not reasonably be carried out without the waiver or alteration.

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the basic elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research, or the component of the research related to the proposed waiver or alteration of consent, involves no more than minimal risk to the subjects and is reasonable in relation to the benefits of the research;
(2) When the request for a waiver involves access to materials (data, documents, records or specimens) the IRB should consider the following:
    a. the minimum necessary information to accomplish the research, including the need for identifiers;
    b. the sensitivity of the information; and
    c. provisions in place to protect confidentiality;
(3) The waiver or alteration of consent has important ethical or scientific justification. For example: (i) scientific validity would be compromised if consent was required because it would introduce bias to the sample selection; or (ii) subjects' behaviors or responses would be biased, such that conclusions would not be meaningful; or (iii) the consent procedure would itself create additional threats to privacy that would otherwise not exist, or there is risk of inflicting psychological, social or other harm by contacting individuals or families;
(4) The waiver or alteration of consent should not be justified solely on the basis of convenience, cost or speed; and
(5) Whenever appropriate, subjects will be provided with previously undisclosed information, when such information is pertinent to their involvement.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.

Attachment D. Recommendations Regarding Informed Consent and Waiver of Consent, as Revised

Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Secretary Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a recommendation relative to Department of Health and Human Services Regulation for the Protection of Human Subjects as codified in 45 CFR Part 46. This letter represents the xxx in a series of recommendations from SACHRP.

The informed consent requirements found in HHS 45 CFR 46 Regulation for the Protection of Human Subjects in Research provide a bedrock protection for individuals participating in research studies. While the regulatory default for non-exempt research is to obtain and document the informed consent of all participants, the regulations anticipated scenarios where this default requirement would be inappropriate given the proposed **research** methods~~**ology**~~, the context in which the research would be conducted or the subject population. The regulations included provisions allowing IRBs to waive some or all elements of informed consent when specific conditions have been met.

In practice, the regulations governing waivers of informed consent at §46.116(d) are constructed in such a way that **many** IRBs ~~have variable understanding of when waivers of selected elements of consent are appropriate. As a result, IRBs have frequently~~ require~~d~~ investigators to include information in consent documents that adds little **or no** value to the consent process, for example, a statement that "the only alternative is not to participate in this research." In fact, by adding length to consent documents and including irrelevant information it could be argued that the effectiveness of the consent process is diminished. In addition, IRBs struggle to interpret whether and how the criteria should be applied in order to grant a full waiver of informed consent.

SACHRP proposes modification of 45 CFR Part 46.116 in order to: (1) ~~consolidate~~ **reorganize** the elements of informed consent at §116 (a) and (b) ~~into one comprehensive list of elements;~~ (2) empower IRBs to waive selected elements of consent when **they** deem~~ed~~ appropriate ~~by the IRB~~; and (3) clarify the circumstances in which an IRB may grant a complete waiver of informed consent.

The proposed restructuring of 45 CFR Part 46.116 would not erode the ethical foundation embodied in informed consent. Modification of the regulations would instead permit IRBs to more ~~consistently~~ **appropriately** grant partial or complete waivers of informed consent without impinging on the ethical validity of the consent process or the research itself. These waivers are already permitted in the existing regulations, but nuances in the language have deterred IRBs from exercising the flexibility that the regulations were intended to provide.

Therefore, SACHRP recommends the following new language for inclusion in 45 CFR 46. **Note that FDA regulations (21 CFR 50) do not provide for an analogous waiver of informed consent; to the**

extent that the elements below are also found in FDA requirements for informed consent, the same recommendations should be considered.

§46.116 General requirements for informed consent.
Except as provided elsewhere in this policy, no investigator may involve a human being as a subject in research covered by this policy unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

In considering the elements of informed consent to be provided to subjects, the focus should be on those activities, risks and benefits that are specific to the research (as distinguished from the activities, risks and benefits that subjects would experience if not participating in the research)

*(a) ~~Basic elements of informed consent.~~ Except **when waived under** ~~as provided in~~ paragraphs (c) or (d) of this section, in seeking informed consent the following information shall be provided to each subject:*

*(1) A statement that the study involves research, an explanation of the purposes of the research, a description of **research-related** ~~procedures~~**activities** ~~that subjects will be asked to undergo~~ with emphasis on those ~~procedures~~ **activities** that are directly relevant to **an informed** decision to participate, and identification of any **activities** that are experimental;*
*(2) A description of **those** foreseeable risks or discomforts **about which a reasonable potential subject would want to know due to the probability or seriousness of their occurrence;***
*(3) A description of any benefits to the subject or to others which may reasonably be expected from the research; **if there are no direct benefits expected for subjects, this should be stated;***
(4) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights; and
*(5) A statement that participation is voluntary, **refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled,** and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.*

*(b) ~~Optional elements of informed consent.~~ When **the IRB determines tha**t one or more of the following elements of information **are material to prospective subjects' decisions to participate, the elements shall** be provided to each subject. In the event **one or more of the following elements** is not to be included, it is not necessary to determine or document that the waiver criteria under paragraph (c) or (d) of this section are met:*

(1) A disclosure of appropriate alternative procedures or courses of treatment, that might be advantageous to the subject;
(2) A statement describing the extent to which confidentiality of records identifying the subject will be maintained;

(3) A statement of whether ***compensation,*** *medical treatment,* ***or payment for that medical treatment*** *is available if injury occurs, where further information may be obtained, and whom to contact in the event of a research-related injury to the subject.*
(4) A statement that ~~the particular treatment or procedure~~ ***research*** *may involve risks ~~to the subject (or to the embryo or fetus, if the subject is or may become pregnant)~~* ***that*** *are currently unforeseeable;*
(5) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent;
(6) Any additional costs to the subject that may result from participation in the research;
(7) The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject;
(8) A statement that significant new findings developed during the course of the research that may relate to the subject's willingness to continue participation will be provided to the subject;
*(9) The approximate number of subjects involved in the study****; and***
(10)The expected duration of the subject's participation.

(c) An IRB may approve a consent procedure which does not include, or which alters, some or all of the basic elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designated to study, evaluate, or otherwise examine: (i) public benefit or service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs; and
(2) The research could not reasonably ***be*** *carried out without the waiver or alteration.*

(d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the basic elements of informed consent set forth in this section, or it may waive the requirement to obtain informed consent provided the IRB finds and documents that:

(1) The research, or the component of the research related to the proposed waiver or alteration of consent, involves no more than minimal risk to the subjects ~~and is reasonable in relation to the benefits of the researc~~h. When the request for a waiver involves access to materials (e.g. data, documents, records or specimens) the IRB should consider the following:
    a. the minimum necessary information to accomplish the research, including the need for identifiers;
    b. the sensitivity of the information; and
    c. the provisions in place to protect confidentiality;
(2) ***The research could not reasonably be carried out without the waiver or alteration. Appropriate ethical or scientific rationales might includ****e, for example: (i) scientific validity would be compromised if consent were required because it would introduce bias to the sample selection; or (ii) subjects' behaviors or responses would be* ***altere****d, such that* ***study*** *conclusions would be* ***biased****; or (iii) the consent procedure would itself create additional threats to privacy that would otherwise not exist; or (iv) there is risk of inflicting* ***significant*** *psychological, social or other harm by contacting individuals or families.* ***Once the IRB*** *~~The waiver or alteration of consent should not be justified solely on the basis of~~*

~~*convenience, cost or speed;*~~ ***has determined that the waiver or alteration does not adversely impact the ethical nature or scientific rigor of the research, logistical issues (e.g. cost, convenience, speed) may be considered;*** *and*

(3) ***When appropriate, subjects will be provided with*** *previously undisclosed information* ***about the nature of the study following their participation***.

(e) The informed consent requirements in this policy are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

(f) Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted ***or required*** *to do so under applicable federal, state, or local law.*

Attachment E. SACHRP Recommendation on IRB Knowledge of Local Context with Respect to Increasing Use of Single IRB Review, as Presented

SACHRP recognizes that there is more use of single IRBs for review for multi-site studies and single site studies that are reviewed by an IRB external to the site where the research is conducted. Even so, institutions are still often reluctant to cede authority for IRB review and those IRBs that review regularly at sites external to them, i.e., independent IRBs and central IRBs, have developed additional procedures to address local context that are burdensome and rarely provide information useful to reviewing the research. These concerns apply to all types of research, not just clinical research. For example, it applies to social behavioral research such as in the fields of anthropology and social work and other areas such as epidemiological research. It is believed that the current practices are in part the consequence of guidance from OHRP and FDA.

SACHRP commends OHRP for the actions it has taken recently to clarify the Office's view regarding local context. OHRP has archived its 1998 guidance on Knowledge of Local Context, and has issued a letter dated April 30, 2010, which clarifies that OHRP fully agrees with the Food and Drug Administration's position on the benefits of relying on a single central IRB for multicenter research. OHRP also addressed the issue of non-local IRB review at the SACHRP meeting of July 2012.

The FDA's 1998 Information Sheet on local context is out of date and should be archived, but FDA's 2006 guidance on the use of central IRBs ("Using a Centralized IRB Review Process in Multicenter Clinical Trials,") only needs some minor updates.

In the historical context of IRB review in the United States, there traditionally has been great tolerance for local diversity of opinion among local IRBs, which have been encouraged to exercise their freedom to reach decisions based on local circumstances and preferences. Further, by regulation and design, IRBs generally operate as "courts of last resort," as their decisions are most often final and binding.[1] When this system was developed, most research was conducted at a single site, and study designs were individual and unique. In recent years, however, particularly in biomedical research, studies across many sites increasingly share a common study design, having been designed and funded by industry or federal agencies in this way, specifically in order to assure adequate and representative participant enrollment. In a multi-site study, in which sites share a common study design, the risk profile of the study has many more commonalities than differences among the participating sites.

For such studies, the value of local variability ebbs in importance. What become more important, to assure both safety of subjects and scientific value, is that these sites adhere to a common study design and that information about any adverse events/unanticipated problems be analyzed in common and by those with specialized expertise, with findings shared promptly and uniformly across all sites. Because the research environment – at least in these sorts of studies – has drastically changed, but because significant differences among sites and local subject populations can remain, SACHRP recommends that FDA and OHRP develop unified guidance that facilitates single IRB review, and assures adequate consideration of true local differences, for studies in which a common study design and unified review will tend to yield better science and greater subject safety. The use of single IRBs can improve quality

[1] Federal authorities of cognizant jurisdiction (e.g., OHRP, FDA, funding agencies) may overturn IRB decisions, but such actions are infrequent and are regarded as exceptional. In addition, in institutions or entities in which research is conducted, the institutions or entities themselves may forbid research from being initiated, even when an IRB has approved the research; but the institutions or entities may not allow research that an IRB has disapproved.

in these ways, and not just reduce administrative burden, but true local variations in risk must continue to be recognized and accommodated in study design and conduct.

The term "single IRB review" refers to a variety of types of IRBs, with the unifying feature being review of research, regardless of location, by a single IRB. The single IRB can be of several models, such as institution based, independent, central, collaborative, or lead. The term includes IRBs that are the focus of reliance agreements such as Harvard and the Ohio consortium. Central IRBs, such as the NCI and VA central IRBs and independent IRBs, are a subset of single IRBs.

SACHRP recommends that OHRP and FDA issue guidance or FAQs or use another mechanism that harmonizes the use of single IRB review. Such guidance should be applicable to any type of IRB that is at a different location from the research site. To accomplish this goal, SACHRP recommends that FDA make minor modifications to its 2006 guidance on central IRB review. SACHRP also recommends that OHRP issue guidance, by the most practical means, which mirrors as closely as possible the revised 2006 FDA guidance on central IRB review.

The minor revisions to the 2006 FDA guidance should be the removal of footnote 12, which references the archived OHRP guidance, and footnote 13, which references out of date FWA information. The FDA should also harmonize more closely the current sections V and VI so that there is similar guidance for institutions with and without internal IRBs, and less emphasis on the concept of facilitated review introduced by the NCI Central IRB. Finally, SACHRP recommends that FDA add a footnote noting that "central IRBs" are a subset of "single IRBs," and that single IRB review of research should be encouraged for multi-site research and other such situations as well.

After FDA makes these minor changes to the 2006 guidance, OHRP should by the most practical means issue corresponding guidance.

Consistent with 45 CFR 46 (the HHS regulations), FDA regulations, and the FDA 2006 guidance, "the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice." The revised guidance documents should address, but not be limited to, four key topics that are important for all IRBs : applicable law and local standards , knowledge of institutional policies and capacity, investigator and study staff qualifications, and community and subject considerations.[2] In contrast to prior guidance, the guidance should describe what the IRB must consider rather than dictate procedural requirements.. Often the relevant information can be obtained through the application process and the standard IRB procedures. However, it is important for the IRB to have written procedures and to be prepared to obtain additional information when appropriate, such as through consultation with other parties. IRBs should have flexibility to obtain this information in the most efficient manner, and given the pace of technological change it is not effective for guidance to recommend specific administrative measures.

Applicable Law and Local Standards

Both HHS and FDA regulations require that "the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards

[2] This applies to equally to local IRBs that approve research at the same site where the research is conducted, but the focus of this document is review by IRBs located at a different site from where the research is conducted.

of professional conduct and practice." For any IRB review, including single IRB review of research at an external site(s), the IRB should have access to and consider state and other applicable law.

It would be valuable to IRBs to have access to a public state law data base. SACHRP encourages the development of such a data base.

Knowledge of Institutional Policies and Capacity

As noted above, HHS and FDA regulations require that, among other considerations, "the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments...." For any IRB review, the IRB should have access to and consider institutional capacity, commitments and policies. Institutional capacity includes the resources to support the research such as space, equipment, and personnel. Institutional commitments include policies on issues such as birth control, compensation for injury, or contacts for research subjects' questions.

Investigator and Study Staff Capability

The investigator and study staff should be appropriately qualified to conduct the research through knowledge and experience. When an IRB is reviewing research external to itself, additional efforts may be required to assess the investigator and study staff. The IRB should either assess investigators and study staff itself, or rely upon alternative measures such as an institutional credentialing/privileging process. The IRB should also have access to information about prior research non-compliance, criminal activities, state board issues, etc. Other factors to be considered in assessing qualifications include financial conflicts of interest, research workload, and training in research ethics and the conduct of research.

Community and Subject Considerations

The IRB should have access to information about the prospective subject population. Often some or all of this information will be in the protocol or the IRB application materials. Other times the IRB will need supplemental information such as census data, including race/ethnicity, primary languages, and religious affiliations.

The IRB will need to also have procedures that address extra steps taken for research involving unique cultures and sensitive areas of inquiry, particularly when reviewing non-local research.

SACHRP believes that these changes to guidance will help to increase reliance on single IRB review, which in turn will promote quality and efficiency in human subject protections.

Attachment F. SACHRP Recommendations on Consideration of Local Context with Respect to Increasing Use of Single IRB Review, as Revised

SACHRP recognizes that there is **increased** use of single IRBs for review for multi-site studies, **as well as for** single site studies that are reviewed by an IRB external to the site where the research is conducted. ~~Even so, institutions are still often reluctant to cede authority for IRB review and those IRBs that review regularly at sites external to them, i.e., independent IRBs and central IRBs, have developed additional procedures to address local context that are burdensome and rarely provide information useful to reviewing the research~~. ~~These concerns apply~~**This increased use of single IRBs applies** to all types of research, not just clinical research. For example, it applies to social behavioral research such as in the fields of anthropology and social work and other areas such as epidemiological research. ~~It is believed that the current practices are in part the consequence of guidance from OHRP and FDA.~~

SACHRP commends OHRP for the actions it has taken recently to clarify the Office's view regarding local context. OHRP has archived its 1998 guidance on Knowledge of Local Context, and has issued a letter dated April 30, 2010, which clarifies that OHRP fully agrees with the Food and Drug Administration's position on the benefits of relying on a single central IRB for multicenter research. OHRP also addressed the issue of non-local IRB review at the SACHRP meeting of July 2012.

The FDA's 1998 Information Sheet on local context is out of date and **SACHRP recommends that it be archived, and FDA's 2006 guidance on the use of central IRBs ("Using a Centralized IRB Review Process in Multicenter Clinical Trials,") would benefit from minor updates**.

In the historical context of IRB review in the United States, there traditionally has been great tolerance for diversity of opinion among local IRBs, which have been encouraged to exercise their freedom to reach decisions based on local circumstances and preferences. Further, by regulation and design, IRBs generally operate as "courts of last resort," as their decisions are most often final and binding.[1] When this system was developed, most research was conducted at a single site, and study designs were individual and unique. In recent years, however, ~~particularly in biomedical research,~~ studies across many sites increasingly share a common study design, having been designed and funded by industry or federal agencies in this way. In a multi-site study, in which sites share a common study design, the ethical concerns and risk/benefit profile of the study have many more commonalities than differences among the participating sites.

For such studies, the value of local variability ebbs in importance. What becomes more important, to assure both safety of subjects and scientific value, is that these sites adhere to a common study design and that information about any adverse events/unanticipated problems be analyzed in common and by those with specialized expertise, with findings shared promptly and uniformly across all sites. Because the research environment – at least in these sorts of studies – has drastically changed, and significant differences among sites and local subject populations can remain, **SACHRP recommends that FDA**

[1] Federal authorities of cognizant jurisdiction (e.g., OHRP, FDA, funding agencies) may overturn IRB decisions, but such actions are infrequent and are regarded as exceptional. In addition, in institutions or entities in which research is conducted, the institutions or entities themselves may forbid research from being initiated, even when an IRB has approved the research; but the institutions or entities may not allow research that an IRB has disapproved.

and OHRP develop unified guidance that facilitates single IRB review, and assures adequate consideration of material local differences, for studies in which a common study design and unified review will tend to yield better science and greater subject safety. The use of single IRBs may improve quality and reduce administrative burden, but material local variations must continue to be recognized and accommodated in study design and conduct.

The term "single IRB review" refers to a variety of types of IRBs, with the unifying feature being review of research, regardless of location, by a single IRB. The single IRB can be of several models, such as institution based, independent, central, collaborative, or lead. The term includes IRBs that **engage in** reliance agreements such as Harvard and the Ohio consortium. Central IRBs, such as the NCI **central IRBs**, the VA Central IRB, and independent IRBs, are a subset of single IRBs.

SACHRP recommends that OHRP and FDA issue guidance or FAQs or use another mechanism that harmonizes the standards governing the use of single IRB review. Such guidance should be applicable to any type of IRB that is at a different location from the research site. To accomplish this goal, **SACHRP recommends that FDA make minor modifications to its 2006 guidance on central IRB review. These include the removal of footnote 12 that references the archived OHRP guidance, and footnote 13 that references out of date FWA information. The FDA should also harmonize more closely the current sections V and VI so that there is similar guidance for institutions with and without internal IRBs, and less emphasis on the concept of facilitated review introduced by the NCI central IRBs. Finally, the FDA should add a statement noting that "central IRBs" are a subset of "single IRBs," and that single IRB review of research should be encouraged for multi-site research and other such situations as well.**

SACHRP recommends that OHRP issue guidance, by the most practical means, that mirrors as closely as possible the revised 2006 FDA guidance on central IRB review. ~~After FDA makes these minor changes to the 2006 guidance, OHRP should by the most practical means issue corresponding guidance.~~ Consistent with 45 CFR 46 (the HHS regulations), FDA regulations, and the FDA 2006 guidance, "the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice." The revised guidance documents should address, but not be limited to, four key topics that are important for all IRBs: applicable law and local standards, knowledge of institutional policies and capacity, investigator and study staff qualifications, and community and subject considerations.[2]

In contrast to prior guidance, the guidance should describe what the IRB must consider rather than dictate procedural requirements. Often the relevant information can be obtained through the application process and the standard IRB procedures. However, it is important for the IRB to have written procedures and to be prepared to obtain additional information when appropriate, such as through consultation with other parties. IRBs should have flexibility to obtain this information in the most efficient manner, and given the pace of technological change, **SACHRP suggests that the guidance avoid recommending** specific administrative measures.

[2] This applies to equally to local IRBs that approve research at the same site where the research is conducted, but the focus of this document is review by IRBs located at a different site from where the research is conducted.

Applicable Law and Local Standards

Both HHS and FDA regulations require that "the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice." For any IRB review, including single IRB review of research at an external site(s), the IRB should have access to and consider state and other applicable law.

It is critical for ~~would be valuable to IRBs to~~ **IRBs to** have access to a **compendium of** state law **relevant to human subject research**. **SACHRP recommends that the Secretary of HHS support the development and maintenance of such a compendium and other resources to support single IRB review.**

Knowledge of Institutional Policies and Capacity

As noted above, HHS and FDA regulations require that, among other considerations, "the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments...." **SACHRP recommends that the reviewing IRB should have access to and consider institutional capacity, commitments and policies.** Institutional capacity includes the resources to support the research such as space, equipment, and personnel. Institutional commitments include policies on issues such as ~~birth control~~ **contraception,** compensation for injury, or contacts for research subjects' questions.

Investigator and Study Staff Capability

The investigator and study staff should be appropriately qualified to conduct the research through knowledge and experience. SACHRP recommends that when an IRB is reviewing research to be conducted at an external site, the IRB should establish mechanisms (e.g. rely on institutional processes, etc) to assess the experience and qualifications of **investigator and study staff.** ~~**The IRB should either assess investigators and study staff itself, or rely upon alternative measures such as an institutional credentialing/privileging process.**~~ **The IRB should also assess relevant information about prior research non-compliance, criminal activities, state board issues, etc.** Other factors to be considered in assessing qualifications include financial conflicts of interest, research workload, and training in research ethics and the conduct of research.

Community and Subject Considerations

SACHRP recommends that the IRB should assess relevant information about the prospective subject population. Often some or all of this information will be in the protocol or the IRB application materials. Other times the IRB will need supplemental information such as census data, including race/ethnicity, primary languages, and religious affiliations.

SACHRP recommends that the IRB should establish procedures to address research involving discrete and insular ~~**cultures**~~ **communities a**nd sensitive areas of inquiry, particularly when reviewing non-local research.

SACHRP believes that these changes to guidance will help to increase reliance on single IRB review, which in turn will promote quality and efficiency in human subject protections.

Attachment G. SACHRP Comments on OHRP and FDA Draft Guidance Documents Regarding IRB Transfers, As Presented

Transfers of research among institutions and IRBs have been an increasingly common occurrence since 1996. In response, OHRP[1] (May 23, 2012) and FDA[2] (June 12, 2012) have released separate guidance documents regarding the transfer of research to another institutional review board (IRB) or institution. SACHRP commends OHRP and FDA for issuing draft guidance on IRB transfers, which will help to provide consistency and quality to this practice. SACHRP has the following comments regarding these draft guidance documents.

First, SACHRP would like to commend the OHRP and FDA for providing these draft guidance documents. They address an important practice among IRBs, and they are flexible documents that will serve to aid IRBs and institutions in conducting transfers of research activities. The documents appropriately stress that the central goal is to provide continuous IRB oversight of ongoing research, which in turn helps to ensure that subjects are adequately protected.

Second, SACHRP encourages the agencies to issue unified joint guidance. SACHRP recommends that when it is not practical to issue a joint guidance, the agencies issue guidance documents that are as similar as possible in content. In the current draft guidance documents, there are areas where one document is more specific than the other without obvious reasons for the dissimilarities. For instance, the OHRP document provides more detail about the steps to be taken regarding IRB transfers within an institution.

Third, SACHRP recommends that OHRP adopt the approach that FDA has taken on "Transfer of IRB Oversight between Two IRBs in the Same Institution" (Section IV. A). The FDA approach is less complex and equally provides flexibility and guidance on human subject protection, without unduly burdening investigators, IRBs and institutions. This approach would also create closer conformance between the two documents.

Fourth, SACHRP recommends that the table in the OHRP scenario 3 should be incorporated into text format as needed because it is difficult to read and because it is largely repetitive of existing text. This section could also be reduced in length similar to the FDA guidance document.

SACHRP notes that both draft documents recommend the use of a written agreement and suggests that IRBs, not institutions, are responsible for setting up such agreements. Agreements between institutions are generally an institutional responsibility and decision, rather than an IRB responsibility and decision. Both documents should better reflect that this is an institutional responsibility rather than an IRB responsibility.

Fifth, while recognizing that the use of a written agreement and the suggested actions are qualified with the term "as appropriate," SACHRP recommends that OHRP and FDA rephrase the language about the written agreement to stress that the agreement outlines the plan for how the transfer will occur and provides criteria for determining that the transfer is complete. It is often not feasible or

[1] "Considerations in Transferring a Previously-Approved Research Project to a New IRB or Research Institution," online at http://www.hhs.gov/ohrp/newsroom/rfc/pdftransferdraftdoc.pdf.

[2] "Draft Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors: Considerations When Transferring Clinical Investigation Oversight to Another Institutional Review Board," online at http://www.gpo.gov/fdsys/pkg/FR-2012-06-12/pdf/2012-14295.pdf.

necessary to address all of the eight recommended actions in advance in a written agreement, as many of them will be case-dependent. SACHRP recommends that the agencies instead say, "When transferring IRB review and oversight of research projects from one IRB to another IRB, OHRP recommends that a plan for the transfer process be documented in a written agreement between the original and receiving IRBs, if appropriate. The agreement should address how the IRBs document the following eight actions, as appropriate. We describe each of these actions in more detail below."

Sixth, SACHRP also believes that the parenthetical "Note" in the "Introduction" section of the OHRP draft should be revised to specifically to change "may not" to "normally will not", as follows: "[Note: OHRP recognizes that for transfers of oversight between IRBs at the same institution, a written agreement *normally will* not be necessary as the process may be addressed by the institution's established procedures (assuming all appropriate steps as identified below are covered). However, the transfer should be appropriately documented, or addressed in written policies.]"

Seventh, when research projects are transferred from an institution, consideration should be given to local law. IRBs and institutions often are required by state law or institutional policy to limit the access to their records and may only share records in circumstances where the requesting party has a regulatory or legal right to review them.

Eighth, SACHRP recognizes that privacy issues commonly arise in the transfer of data and documents to a new entity. These concerns arise, for example, from HIPAA, state medical privacy laws, state genetic privacy laws, and federal drug and alcohol treatment record laws. SACHRP recommends that the guidance address authorization and waiver considerations, and how entities can proactively plan for potential transfers from a privacy perspective. SACHRP recommends that OHRP and FDA consider inclusion of Office for Civil Rights (OCR) input on HIPAA concerns.

Finally, SACHRP notes that in regards to action six of the guidance documents, it is suggested that there are many ways to notify previously enrolled subjects of the change of IRB, including use of a postcard. For many types of research, use of a postcard would reveal potentially private information to postal clerks, family members, etc. SACHRP suggests that the term "letter" rather than "postcard" would be preferable.

In closing, SACHRP commends OHRP and FDA for issuing draft guidance on IRB transfers, which will help to provide consistency and quality to this activity.

Attachment H. SACHRP Comments on OHRP and FDA Draft Guidance Documents Regarding IRB Transfers, As Revised

Transfers of research among institutions and IRBs have been an increasingly common occurrence since 1996. In response, OHRP[1] (May 23, 2012) and FDA[2] (June 12, 2012) have released separate guidance documents regarding the transfer of research to another institutional review board (IRB) or institution. ~~SACHRP commends OHRP and FDA for issuing draft guidance on IRB transfers, which will help to provide consistency and quality to this practice.~~ SACHRP has the following comments regarding these draft guidance documents.

First, SACHRP would like to commend the OHRP and FDA for providing these draft guidance documents, **which will help to provide consistency and quality to this practice.** They address an important practice among IRBs, and they are flexible documents that will serve to aid IRBs and institutions in conducting transfers of research activities. The documents appropriately stress that the central goal is to provide continuous IRB oversight of ongoing research, which in turn helps to ensure that subjects are adequately protected.

Second, SACHRP encourages the agencies to issue unified joint guidance. SACHRP recommends that when it is not practical to issue a joint guidance, the agencies issue guidance documents that are as similar as possible in content. In the current draft guidance documents, there are areas where one document is more specific than the other without obvious reasons for the dissimilarities. For instance, the OHRP document provides more detail about the steps to be taken regarding IRB transfers within an institution.

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Fifth, while recognizing that the use of a written agreement and the suggested actions are qualified with the term "as appropriate," SACHRP recommends that OHRP and FDA rephrase the language about the written agreement to stress that the agreement outlines the plan for how the transfer will

[1] "Considerations in Transferring a Previously-Approved Research Project to a New IRB or Research Institution," online at http://www.hhs.gov/ohrp/newsroom/rfc/pdftransferdraftdoc.pdf.

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occur and provides criteria for determining that the transfer is complete. It is often not feasible or necessary to address all of the seven recommended actions in advance in a written agreement, as many of them will be case-dependent. SACHRP recommends that the agencies instead say, "When transferring IRB review and oversight of research projects from one IRB to another IRB, OHRP recommends that a plan for the transfer process **be established** between the original and receiving IRBs, if appropriate. The **plan** should address how the IRBs document the following eight actions, as appropriate. We describe each of these actions in more detail below."

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Seventh, ~~when research projects are transferred from an institution, consideration should be given to local law. IRBs and institutions often are required by state law or institutional policy to limit the access to their records and may only share records in circumstances where the requesting party has a regulatory or legal right to review them.~~ SACHRP recognizes that privacy issues commonly arise in the transfer of data and documents to a new entity. These concerns arise, for example, from **institutional policy**, HIPAA, state medical privacy laws, state genetic privacy laws, and federal drug and alcohol treatment record laws. SACHRP recommends that the guidance address authorization and waiver considerations, and how entities can proactively plan for potential transfers from a privacy perspective. SACHRP recommends that OHRP and FDA consider inclusion of Office for Civil Rights (OCR) input on HIPAA concerns.

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~~In closing, SACHRP commends OHRP and FDA for issuing draft guidance on IRB transfers, which will help to provide consistency and quality to this activity.~~

Attachment I. Considerations and Recommendations Concerning Internet Research and Human Subjects Research Regulations, with Revisions

Introduction:

The purpose of this document is to provide a starting point for the development of FAQs and/or Points to Consider regarding the conduct and review of Internet research. Current human subjects regulations, originally written over thirty years ago, do not address many issues raised by the unique characteristics of Internet research. Some IRBs, concerned about their ability to make appropriate and responsible decisions regarding Internet research, have developed working guidelines for investigators.[1] Many of these guidelines focus on technical questions about data security, but there are other issues to address: basic categorizations of types of Internet research; types of data; data identifiability and subject privacy; appropriate consent and authentication of subjects procedures; jurisdictional authority; appropriate data security practices, including data collection, research administration, and data destruction; data sharing practices and implications; and discussion of what is common, reasonable, and acceptable in a given Internet environment and how these standards relate to current regulations and guidance in the areas of informed consent, recruitment, and risk of harm.

Ethical conduct of Internet research also brings questions of scientific design into high relief: authenticity of subject identity, assurance of comprehension of consent, and verification of data integrity can present significant challenges.

Forms and Examples of Internet Research:

There are multiple forms of Internet research. Some experiments are conducted fully in online fora or conditions; some research may include elements conducted through the Internet, for example, using a social media application as a recruitment tool combined with traditional research methods and spaces; some research can only be conducted on the Internet, for example, an ethnography of an online-only forum that has no corresponding geo-physical location; or, the Internet may be a tool underlying data collection. We identify a range of Internet research where human subjects may be involved:

- Research studying information that is already available on or via the Internet without direct interaction with human subjects **(harvesting, mining, scraping**[2]**—**observation or recording of otherwise-existing data sets, chat room interactions, blogs, social media postings, etc.)

- Research that uses the Internet as a vehicle for recruiting or interacting, directly or indirectly, with subjects (Self-testing websites, survey tools, **Amazon Mechanical Turk®,** etc.)

- Research about the Internet itself and its effects (use patterns or effects of social media, search engines, email, etc.; evolution of privacy issues; information contagion; etc.)

[1] See for example: http://irb.uconn.edu/Internet_research.html

—http://www.marianuniversity.edu/interior.aspx?id=13714

—http://inside.bard.edu/irb/guidelines/

—http://www.luc.edu/irb/irbonlinesurveys2.shtml

—http://www.research.psu.edu/policies/research-protections/irb/irb-guideline-10

[2] Terms that may be unfamiliar are highlighted in blue bold and included in the Glossary.

• Research about Internet users—what they do, and how the Internet affects individuals and their behaviors

• Others (emerging and cross-platform types of research and methods, including m-research (mobile))[3]

- Recruitment in or through Internet locales or tools, for example social media, push technologies

The broad and overarching term "Internet research" includes both the Internet as a *tool for research* and the Internet as a *locale or venue of research*. For example, research employing survey instruments, search engines, databases, databanks, or aggregators would constitute using the Internet as a tool for research. Such research may not involve direct interaction with human subjects, but identifiers or personally identifiable information may be generated, collected, and/or analyzed. In contrast, using the Internet as a medium or locale of research entails qualitative or quantitative studies of various Internet "spaces," such as chat rooms, gaming worlds, virtual environments, or other simulated locales. Internet phoning, video conferencing, or online chat may be both tool and venue; applications such as Skype® or Facetime® may be used to contact subjects or participants, and interviews or focus groups can be conducted via the application. The increasing predominance of social media, defined as a "group of Internet-based applications that build on the ideological and technological foundations of Web 2.0, and that allow the creation and exchange of user-generated content,"[4] is blurring the tool-versus-venue model. Consider, for example, research using a social media application that engages subject recruitment via targeted ads on such platforms as Facebook® or via **microblogging** tools such as Twitter®, uses online data collection and analytic tools, and disseminates data via other social media applications. A specific example comes from an ongoing exploratory group of the ASCO Integrated Media and Technology Committee, which is reviewing the regulatory, legal, and ethical implications of oncology research and social media usage.[5] Projects using community-based participatory research methods are embracing Internet and m-research to send, receive, collect, and disseminate data synchronously. Other examples include such applications as CenceMe®, which integrates with social media and cellular devices to "infer a person's activity…and social context. This information is shared within the person's social circle…."[6]

Clear boundaries between **"grid-enabled"** technologies are eroding. For example, mobile applications interface with Internet sites or venues; tablets connect with cloud-based services in the use of survey tools; mobile devices are used in conjunction with Internet-enabled methods such as momentary sampling, reverse RSS data feeds, or synchronous data collection and analysis. With the emergence of such cross-operational research, fundamental aspects of human subjects research (recruitment,

[3] Much discussion is occurring around FDA approval of mobile applications for medical research. In July 2011, the FDA released draft guidance for Industry and Food and Drug Administration Staff - Mobile Medical Applications available at http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm263280.htm#5

[4] Kaplan, Andreas M.; Michael Haenlein (2010) "Users of the world, unite! The challenges and opportunities of Social Media". Business Horizons 53(1): 59–68.

[5] Dizon, D. *et al*. (2012). Practical guidance: The Use of Social Media in Oncology Practice. *Journal of Oncology Practice, 000610*.

[6] Miluzzo, E. *et al.* (2010). Research in the App Store Era: Experiences from the CenceMe App Deployment on the iphone." *ACM, 978-1-60558-843-8-10/09*

informed consent, data identifiability) present new challenges. Consent, for example, may occur in a synchronous setting, where both investigator and subject share a virtual space; or, consent may occur asynchronously, where a consent form is posted and subjects review it in the absence of the investigator. In the latter case, best practices are needed to ensure appropriate comprehension of consent documents and processes.[7] Thoughtful IRB review of emerging forms of cross-platform, cross-operational research may increasingly demand technical expertise in addition to regulatory knowledge, as new methodologies complicate risk/benefit analyses and issues of confidentiality, privacy, and voluntariness.

This document argues for a reasoned and balanced approach to review of Internet research protocols, and does not advocate for more stringent review of Internet research ~~than of its on-ground counterparts.~~ Nevertheless, in some circumstances researchers/investigators may have additional responsibilities. The ease with which sensitive data can be accessed, shared, hacked, and/or replicated is unique to Internet research, and for this reason, investigator responsibilities for good data stewardship, and heightened awareness of subjects' privacy, confidentiality, and identities, **are critical.**

This document is based on input from the research and professional literature, multiple years of workshops at Public Responsibility in Medicine and Research (PRIM&R) Advancing Ethical Research conferences, on-site panels at SACHRP in 2010 and 2012, and telephone sessions with members of the SAS and SOH subcommittees of SACHRP in 2012. **Based on these experiences, we recommend that OHRP commit to producing formal FAQs or Points to Consider for the research and IRB community along the lines of what is presented below.** In addition, suggestions were made to provide IRBs with lists of appropriate questions to ask when reviewing Internet research, lists of appropriate or acceptable characteristics of vetted third party tools,[8] terms and phrases to use in protocols and informed consent/information sheet documents, a glossary of terms frequently used in Internet research,[9] as well as a decision-making flow chart that resembles existing models. Most of these are still in development.

Fundamental Principles

Investigators and IRBs should remember that the Belmont Report's fundamental principles of respect for persons, beneficence, and justice are as applicable to Internet research as they are to any other form of human subjects research. Regardless of how the regulations may be interpreted in individual studies, adherence to these fundamental principles is important to encouraging public trust in the ethical conduct of Internet research.

Regulatory Considerations
Q1: What is "research involving human subjects" on the Internet?

The regulatory definitions of *research*, *human subject*, and *identifiable private information* must be our starting points.

[7] For example, electronic comprehension checks (quizzes or short responses) of a consent document may be embedded prior to a subject's entrance into a study site or prior to engaging in any research activities. In some studies, subjects must score 100% accuracy on their comprehension checks to be eligible for the research.
[8] Given the frequency with which commercial tools change their terms of service, this list would of necessity be based on appropriate characteristics, rather than calling out specific companies or products.
[9] See Appendix A

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Human subject means a living individual about whom an investigator (whether professional or student) conducting research obtains

(1) Data through intervention or interaction with the individual, or
(2) Identifiable private information.

…

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.[10]

Use of the Internet as a tool for research and for intervention or interaction with subjects does not, in general, challenge the definition of "human subject." However, new forms of identity, including **avatars** or other Internet personae, can **be considered as virtual representations of "human subjects"** if personally identifiable information about living individuals can be obtained by observing the actions of, or interacting with, the avatars. Investigators should determine if the avatar is a proxy for the individual, and if so, whether the subject's personally identifiable information (PII) or protected health information (PHI) is being obtained. Some avatars, for example, are simply computer-generated characters or representations and have no connection to an individual's PII/PHI. Other forms of Internet personae, including *bots*, typically do not display PII or PHI. Bots may be programmed to mine or harvest discrete PII from individual profiles, web sites, etc., or they may harvest large collections of data, such as patterns of search behaviors. If a bot's purpose is to collect and display an individual's PII or PHI, it may itself be a proxy for a "human subject." If its purpose is to harvest multiple individuals' PII from multiple sources, its activity might constitute human subjects research (but the bot itself would not be considered a human subject). Depending on the nature of the data and how they are obtained, these entities' activities may or may not require IRB review. (See also footnote 11.)

The issues of "identifiability" and of "private information" are addressed below (see Q3 and Q4).

Q2: What is exempt research involving human subjects on the Internet?

If we grant that a contemplated activity is research involving human subjects, when might it be considered exempt? The use of the Internet to deliver educational materials is now common, and the regulatory exemption at 46.101(b)(1) for certain types of education research will often apply. (See Q8 for further discussion of "normal educational practice.") The exemption at 46.101(b)(2) for certain kinds of tests, surveys, interviews, or observation of public behavior, where the collected information is not sensitive or is not identifiable, is much more complicated; the complications hinge on the issues of "public behavior" and "identifiable." (See Q3, Q4, Q6, and Q7.) The exemption at 46.101(b)(4) raises similar questions about "publicly available" information and the identifiability of subjects,

[10] 45 CFR 46.102(d) and (f)

which are addressed below at Q3 and Q4.

~~Examples of nonexempt research include online clinical trials, research with identified members of vulnerable populations, such as prisoners or children, and some research involving sensitive identifiable information.~~

Q3. When, if ever, is information available via the Internet "private information," and when can subjects "reasonably expect" their private information will not be made public?

Private information as defined in the Common Rule means "information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record)." [45 CFR 46.102(f)]

If individuals intentionally post or otherwise provide information via the Internet**, such information should be considered public unless** existing law and the privacy policies **and/or terms of service** of the entity/entities receiving or hosting the information will, in the first instance, determine whether the information should be considered "private." **To the extent that terms of service or explicit prohibitions would preclude the use of data on the Internet for research purposes, the determination that such data should be considered "private" is clear. In addition, investigators should note expressed norms or requests in a virtual space, which – although not technically binding – still ought to be taken into consideration.** [11] **When in doubt about whether to consider data public or private, investigators are encouraged to consult with their IRB about the specific circumstances.**

~~Some venues on the Internet have explicit statements regarding their privacy policies and whether information they receive and/or provide is considered public or private. Researchers should acknowledge those expectations. Individuals' expectations of privacy may be high if the topic or focus of a forum is sensitive. For example, members of a health-related topic forum or site may have a higher expectation of privacy than members posting to a forum about woodworking or pet care.~~

[11] For example, "Everyone is welcome on PrettyThin. Anorexics, ex-anorexics, people in the health profession….it's an open forum. The alternative is the closet…is that the society we wish to live in?" (http://www.prettythin.com/category/frequently-asked-questions/). However, a different approach is offered at Ana Boot Camp: "Some images, links text and thinspiration may be considered triggering in nature. As well, if you are looking to get anorexia / bulimia by being here then **please leave now**. You will not find information contained within this web site, forum, or any site linked to / from this website on how to become anorexic or bulimic.
If you do not accept the condition of anorexia / bulimia / other eating disorders plus the pro-ana pro-mia movement then you must also leave this proana website immediately. Also you will not use this pro-ana pro-mia web site and or forum against anyone in any conceivable manner. You have been forewarned. By entering this proana promia web site you are signing a digital certificate stating that you have read and understand the above mentioned conditions and you are entering this proana promia site knowingly and willingly of the aforementioned conditions. Entering by any other circumstance is perjury and can be punishable by law." (http://anabootcamp.weebly.com/)

[Note: The following questions are moved to Question 3 from Question 4.]

(a) Are there now, or should there be, consensus standards for privacy of information on the Internet? The regulatory definition of private information cites medical records as an example. Tax records or personal diaries are often also given as examples. Is it possible to define categories of information on the Internet that are, by default, private and others that are, by default, public? For instance, at one extreme, identifiable information that is available only with a subject's permission, or by using a password or other access mechanism under the subject's control, could be considered private. At the other extreme, information that is legally available to any Internet user, without special authorization or access permission, could be considered public.

(b) A subject's own expectation of privacy is not always "reasonable." A subject may assume—perhaps in ignorance—that his or her information provided or available on the Internet is private, but the first part of the regulatory definition of "private information" specifies that the individual "can reasonably [sic] expect that no observation or recording is taking place." Information that is archived online has, *ipso facto*, been recorded. Can it ever be *reasonable* to expect otherwise, absent an explicit statement that no information will be recorded?

(c) Despite (b) above, the Belmont principle of beneficence may support a more conservative approach. A subject who incorrectly assumed his/her identifiable information was private, or restricted only to a select group, might not have posted the information on some social networking site if s/he thought the information would be widely available, believing that the information could be embarrassing or damaging. Do the investigator and the IRB have an obligation to consider the proposed research to be subject to IRB review, even if under existing regulations the research is exempt because the information is publicly available? Researchers and IRBs should consider the nature of the study and the sensitivity of identifiable data; more details about the study, and thoughtful institutional policy, taken in consideration with standard professional or disciplinary norms and practices, would help inform such decisions.

(d) The second part of the definition cites a reasonable expectation that information provided for a specific purpose will not be made public. When is an online venue, or social or professional networking site, or other online activity considered "public"? Does it matter if a password is required to join the venue? If the venue is moderated? If the venue is intended for use by individuals who share a particular condition or interest? Are there "shared priorities" by the members that dictate or determine norms?

One suggestion would be to follow the published privacy/confidentiality policy of the site; if there is no policy the site could be considered public. Privacy policies may parallel "anonymous" meeting standards (e.g., Alcoholics or Narcotics or Gamblers Anonymous), where members operate according to a set of shared priorities and there is an expectation of privacy and confidentiality within *and* outside of the meeting. Investigators should be aware of and respect those shared expectations.

A less nuanced approach would be to say that any venue where membership or participation must be authorized should be considered private. In contrast, venues where any individual can participate without third party approval—even if a password (of the individual's own choosing) is required—would not be considered private. In addition, sites whose purpose is to present participants' comments for public review (such as the comment section follow a

news article) would be considered public even if participants must be vetted or authorized to participate.

~~Some information that would ordinarily be considered private may in fact be deemed public by statute. The Physician Payment Sunshine Act, for example (still awaiting final implementation), mandates sharing of certain data about the financial relationships between doctors, drug companies, and medical device makers. Likewise, new PHS regulations now require public accessibility of certain financial interests of investigators who receive NIH research funding.~~[12]

~~Finally, the HIPAA Privacy Rule~~[13] ~~describes the conditions for release of certain types of health-related information.~~

In addition to Common Rule considerations, there are implications under the HIPAA Privacy Rule. When a HIPAA-covered entity collects individually identifiable health information and then wants to use or disclose the information for research purposes, the Privacy Rule sets conditions on how covered entities may use or disclose protected health information for research purposes (such as requiring the individual's authorization or a waiver of authorization by an IRB) and requires that the information be safeguarded. Note also that the Common Rule and Privacy Rule have different definitions of identifiability, so information that is not considered identifiable under the Common Rule may be identifiable for Privacy Rule purposes.

Q4: What is *identifiable private information* on the Internet?

The Common Rule defines *private information* as "information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record)."[14]

Private information is considered *identifiable* if "the identity of the subject is or may readily be ascertained by the investigator or associated with the information." [45 CFR 46.102(f)]. The nature of online data enables mining and matching, raising the potential for partial identifiers to be combined and individuals recognized.[15] Multiple data sets may be aggregated and analyzed, yielding surprising or novel information. (Existing guidance and best practices regarding genetic databases and biospecimen banks may help inform thinking on these issues.[16])

If the identity of the subject cannot be "readily ascertained by the investigator or associated with the information" then the activity is not research involving human subjects. Unfortunately, the phrase

[12] See 42 CFR 50 Subpart F and http://grants.nih.gov/grants/policy/coi/coi_faqs.htm#G

[13] See http://www.hhs.gov/ocr/privacy/hipaa/administrative/privacyrule/index.html

[14] 45 CFR 46.102(f)

[15] See for example, Sweeny, L. (forthcoming, *Connecting Your Dots: What they know from what you leave behind*; 2004; Privacy-Enhanced Linking. *ACM SIGKDD Explorations* 7(2) December 2005.
Earlier version available as Carnegie Mellon University, School of Computer Science Technical Report CMU-ISRI-05-136. Pittsburgh: November 2000); Narayanan, A. and Shmatikov, V. (2008). Robust De-anonymization of Large Sparse Datasets. In Proc. of *29th IEEE Symposium on Security and Privacy*, Oakland, CA, May 2008, pp. 111-125. IEEE Computer Society.

[16] See, for example, Report of the Public Responsibility in Medicine and Research (PRIM&R) Human Tissue/Specimen Banking Working Group Part I Assessment and Recommendations, 2007 http://oba.od.nih.gov/policy/Tissue%20Banking%20White%20Paper%203-7-07%20final%20combined.pdf

"readily ascertained" is not defined, either in regulations or in guidance, and it is unclear whether the modifier "readily" also applies to "associated with the information." Trying to quantify "readily" in some way, such as "number of clicks needed to get to a name/identity," seems unlikely to be satisfactory.[17]

Q5: What is *intervention or interaction* with a subject in research on the Internet?

Intervention as defined by the Common Rule "includes both physical procedures by which data are gathered … and manipulations of the subject or the subject's environment that are performed for research purposes."[18] Manipulations of subjects can take many different forms, often mimicking "real-world" manipulations,[19] and manipulation of environments may include testing of different website interfaces, provision of different responses to web queries, recording Internet-based activities or behaviors for subsequent analysis, etc., using the Internet as a reminder or interface for the performance of some physical activity (e.g., taking a medication or performing a task), or may be through something as simple as the presence of a researcher.

Interaction includes "communication or interpersonal contact between investigator and subject."[20] Online interaction may occur in environments that range from virtual worlds or guilds to social media sites to chat rooms, newsgroups, and mobile platforms. Environments can be textual and/or graphical. The interaction itself can include, for example, interviews, focus groups, dialogue across a **listserv** or newsgroup, or any exchange via social media. Surveys presented online should be considered "interaction" with subjects, even if there is no live individual receiving responses in real time but data are collected by the survey engine for later access by the investigator. Interaction can also take place via mobile devices, tablets, or other devices that are connected to Internet applications or tools.

Q6. What are the characteristics of purely public sites?

The analogies of public parks and public libraries have been invoked in Internet research, with the idea that just as there should be no expectation of privacy in real-world public settings, so should some Internet-based settings be considered public. However, questions of access, logging and storage and transmission of data, and other technical considerations complicate the comparisons. Further, just as eavesdropping may not be considered appropriate behavior (even if the activity being observed occurs in a public setting), so too may the monitoring of some Internet-based activities raise similar ethical concerns.

In general, purely public sites fall into one or more of the following categories.

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[17] If an IRB considers the expertise or qualifications of the investigator when considering how "readily" an identity can be ascertained, then depending upon the investigator's skill and experience, and availability of other data, use of the same information by two different investigators could in one case constitute research involving human subjects and, in the other, not. This apparent inconsistency, based on researcher expertise or qualifications in Internet research, is not unique to Internet research, but is likely to become increasingly relevant as more and more datasets become available. There has been extensive discussion on the IRB Forum (http://www.irbforum.org) on this issue. See, for example, January 11 – January 25, 2012 discussion on "the meaning of anonymity."

[18] 45 CFR 46.102(f)

[19] See for example, the "Virtual Milgram" at http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0000039.

[20] 45 CFR 46.102(f)

(1) Sites containing information that, by law, is considered "public." In most cases information from these sites will be available without restriction, although access to the information may require payment of a fee. Many federal, state, and local government sites are included in this category: property tax records, birth and death records, real estate transactions, certain court records, voter registration and voting history records, etc.

(2) News, entertainment, classified, and other information-based sites where information is posted for the purpose of sharing with the public.

(3) Open access data repositories, where information has been legally obtained (with IRB approval if necessary) and is made available with minimal or no restriction.

(4) Discussion fora that are freely accessible to any individual with Internet access, and do not involve terms of access or terms of service that would restrict research use of the information.

Q7: What is *observation of public behavior* online?

If an activity (textual, visual, auditory) is legally available to any Internet user without specific permission or authorization from the individual being observed, or from the entity controlling access to the information, the activity should be considered "public behavior." Examples include "comment" postings on news sites; posting on publicly available hosting sites such as YouTube® or Flickr®; postings on classified sites such as Craigslist®; and postings on unrestricted blog or wiki sites. Information posted on social networking sites such as Facebook®, LinkedIn®, Myspace®, or similar fora, and available without restriction to any authorized user of the site, should also be considered "public behavior," even though access to the website itself may be restricted to individuals who have established an account to use the site.[21] Note that the mere fact of an activity being considered "public behavior" does not mean that observation of the activity should automatically be considered exempt from the requirement of IRB review. Per 45 CFR 46.101(b)(2), if the information is recorded in a way that permits identification of subjects, and if disclosure of the identifiable information could "reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation," then the research would not be exempt from IRB review.[22]

Q8: Is online education *normal educational practice?*

Yes, it often is. The exemption at Section 46.102(b)(1) cites "Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods." How far beyond the traditional classroom has the widespread use of personal computers and mobile technologies expanded the range of "commonly accepted educational settings"? There are now

[21] If access to a site is restricted to individuals who must meet specified eligibility criteria, in addition to registering for participation (for instance, individuals who suffer from a particular medical condition), activity on the site should not be considered "public behavior."

[22] The implication of 101(b)(2)—" information obtained is recorded in such a manner that human subjects can be identified…"—is that the information is recorded **by the investigator**. Confirmation of this interpretation would be helpful.

multiple types of online educational practices ranging from complete degree programs, to individual for-credit classes, to activities that supplement regular classroom instruction, to less formal not-for-credit activities such as instructional videos, online lectures, or TED talks. Considerations include the nature of the "education" being provided; the prevalence of a particular intervention in the learning group under consideration; and the existence of the intervention or teaching process prior to a researcher's involvement. The burden of demonstrating that a particular online educational research activity should be exempt from IRB oversight may have to rest with the investigator, but IRBs should understand that the range of Internet-enabled "normal educational practices" continues to broaden.

Q9: When is information *recorded in identifiable manner?*[23]

The exemption at 101(b)(2) refers to "Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation." Is "recorded" in this context limited to data that the investigator records him/herself? ~~Many, perhaps most, Internet sites/tools/venues record~~ **log data** ~~and trails of user data, which include~~ **IP addresses** ~~and other information that may be personally identifiable. If data are collected by survey tools, social media sites, or other services, does that collection meet the regulatory "recorded" standard, even if some information (such as IP address) is not forwarded to the investigator? The FAQ should clarify that the~~ **We believe the intent of this section is** "recorded *by the investigator* in such manner…." (See footnote 22).

~~A strict reading of 101(b)(2) might assume that "can be identified" implies "by any means," since there is no "readily" qualifier, as there is in the definition of "private information." Clarification on this point would be helpful.~~

Q10: When are data, documents, or records *publicly available* on the Internet?

Publicly available may mean:

- Available at no charge to anybody with a computer
- ~~Available to any public citizen~~
- Available to anybody willing to pay the requisite fee
- Available to anybody who meets the terms of a use agreement

Documents that used to be housed in public courthouses or agencies are now often available in electronic form. Such records as state agency reports, property tax assessments, marriage licenses, real estate transactions, voter registration, and the like are now searchable online. Internet tools and sites have simply made access to such public documents easier, but the essential nature of the data is still public.

[23] 101(b)(2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless: (i) information obtained is recorded in such manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.

With the growing availability of data banks and data repositories, and with established data sharing mandates, investigators have greater access to data and data sets. Many IRBs have established exemptions for data shared through **ICPSR,** NIH, NSF, the US Census, etc. Research involving publicly available data sets, with or without identifiers, does not require IRB review under 45 CFR 46.

We may consider these criteria from the United Kingdom's Data Archive, for example,[24] which controls investigator access and the extent to which they are "publicly available":

"For confidential data, the Archive, in discussion with the data owner, may impose additional access controls which can be:

- needing specific authorisation from the data owner to access data
- placing confidential data under embargo for a given period of time until confidentiality is no longer pertinent
- providing access to approved researchers only
- providing secure access to data by enabling remote analysis of confidential data but excluding the ability to download data."

Each of the above bullets would constitute a limitation on public availability and the first three would often preclude applicability of the exemption at 46.101(b)(4).

There have been situations where data are under the control of an individual (or entity) who is unaware of regulatory or statutory restrictions on the sharing of data, or who is aware of the restrictions but nevertheless makes the data available (~~recent i~~ncidents involving WikiLeaks, for example). Investigators and IRBs should ensure that data represented as "publicly available" are, indeed, available without restriction **that would limit the proposed use.**

Q11: How do investigators obtain the informed consent/parental permission/assent of subjects for research on the Internet?

As with other forms of research, the consent/assent process for Internet research should be tailored to the risks and complexities of the research. The absence of direct, in-person contact can add complications to the consent process.

Three oft-cited concerns with consent in Internet research are verifying identification, ensuring comprehension, and obtaining appropriate documentation when needed. Adequate identity verification may in some cases be handled by the hosting survey provider; in other cases, with minimal risk research, it may not be a critical issue. (See Q 15, below.) Comprehension of the consent materials may be addressed by a checkbox ("I understand and agree") for low risk research, or by mandatory quizzes as a comprehension check. The federal ESIGN law authorizes electronic signatures in certain contexts. In other contexts, state law may control. (Note: OHRP is currently working on issues of e-signatures; see Q14)

The consent process for non-exempt online surveys may include a statement that the subject gives evidence of agreement to participate in the research by the fact of his/her completing the survey. This is permissible even if the consent document does not include all the elements prescribed at 45 CFR 46.116(a), so long as the IRB approves a waiver or alteration of some elements under 46.116(c) and

[24] http://www.data-archive.ac.uk/create-manage/consent-ethics/access-control

(d).[25]

When obtaining consent in more than minimal risk research, many steps may be necessary. In one example, an industry-sponsored online Phase IV clinical trial, subjects informed of and interested in participation had to meet eligibility criteria; those who qualified underwent ID/age verification. Consent documents were then emailed, faxed, or made available on a web site, with additional information provided in audio or video format. Subjects were required to take a comprehension quiz after reviewing the consent materials and had to score 100% to move ahead. A designated contact for questions and to provide additional information was available to subjects at all times. Applications such as Skype® or LiveChat® have also been used to enable direct communication between researcher and subject during the consent process.

Research with minors raises particular concerns. There are age verification software products available, which may be of use to researchers. Verification of age can take place through less formal fact-checking embedded in the research instruments (for instance, cross-validating multiple age and birthdate questions). Researchers may advertise only on sites that are age-limited to begin with. Coordinating parental consent with child assent can be difficult, and the Children's Online Privacy and Protection Act (COPPA) mandates parental permission if subjects under the age of 13 are being recruited and they provide identifiable information.[26]

Q12: When may investigators seek to waive or alter the informed consent of subjects in research on the Internet?[27]

Per 46.116 (c) and (d), to waive some or all of the required elements, or to waive the requirement for consent *in toto*, the IRB must find and document:

The research presents no more than minimal risk; the waiver will not adversely affect subjects' rights and welfare; the research could not practicably be carried out without waiver; **and**, when appropriate, subjects will be provided with additional pertinent information after participation.

In the absence of a robust identity verification process, some IRBs will only approve an online consent process under circumstances that meet the criteria for alteration/waiver at 46.116(d), and will consider the age/identity verification difficulties as key to the "impracticability" determination. However, if identifiable information may be collected about children under the age of 13, the COPPA requirement for parental consent will apply (there is no waiver provision).

~~Waiver is not available for FDA-regulated research except for emergency research, and other life-threatening or military situations outlined in FDA regulations at 21 CFR 50.23.~~[~~28~~]

Q13: How do investigators document the informed consent of subjects for research on the Internet?

[25] See http://answers.hhs.gov/ohrp/questions/7249

[26] See http://www.coppa.org/comply.htm; also see FTC's August 1, 2012 proposed changes to COPPA, which includes changes to the COPPA definition of "'person information' to include persistent identifiers" (Ropes & Gray, 2012).

[27] See Subpart A Subcommittee, SACHRP Recommendations Regarding the Provisions for Waiver or Alteration of the Informed Consent Requirements Under Department of Health and Human Services (HHS) Regulations at 45 CFR 46.116(d) (www.hhs.gov/ohrp/archive/.../WaiverConsentDocSAS.doc)

[28] See http://www.fda.gov/RegulatoryInformation/Guidances/ucm126431.htm

According to HHS/OHRP,[29] "For most research, informed consent is documented using a written document that provides key information regarding the research. The consent form is intended, in part, to provide information for the potential subject's current and future reference and to document the interaction between the subject and the investigator. However, even if a signed consent form is required, it alone does not constitute an adequate consent process. The informed consent process is an ongoing exchange of information between the investigator and the subject and could include, for example, use of question and answer sessions, community meetings, and videotape presentations. In all circumstances, however, individuals should be provided with an opportunity to have their questions and concerns addressed on an individual basis."

Appropriate methods for documenting of informed consent in Internet-based research should reflect the risk and complexity of the research. For straightforward minimal risk research, documentation might be in the form of a simple click-through "I agree" statement preceding access to the study materials, where subjects are presented the appropriate consent information and then signal their consent either by checkbox or by completing the survey or experimental materials; this is consistent with OHRP guidance for survey research.[30] When the research protocol is more complicated, or may present more than minimal risk, a signed document, sent via traditional methods or completed via e-signature (see Q 14) may be a necessary component. Investigators can discuss the informed consent process via chat, email, video, or other online venue, such as in a virtual world. Verification of comprehension can be a challenge. Studies may include a "quiz" or survey after the subject reads or listens to the consent script, to confirm their understanding of the presented materials, and only after completion of the comprehension check will a subject proceed to the study site. Other possibilities include a designated chat room or email contact to discuss the consent process and to allow investigators and participants to converse prior to beginning the research.

Also see Q11, Q12 above.

Q14: Can an electronic signature be used to document consent or parental permission?

This question has been answered at http://answers.hhs.gov/ohrp/questions/7249. "Yes, under certain circumstances. First, the investigator and the IRB need to be aware of relevant laws pertaining to electronic signatures in the jurisdiction where the research is going to be conducted.

"Unless the IRB waives the requirement for the investigator to obtain a signed consent or permission form based on the HHS regulations at 45 CFR 46.117(c), a written consent or permission form, which may be an electronic version, must be given to and signed by the subjects or the subjects' legally authorized representatives or the parents of subjects who are children. Some form of the consent document must be made available to the subjects or the parents of subjects who are children in a format they can retain. OHRP would allow electronic signature of the document if such signatures are legally valid within the jurisdiction where the research is to be conducted.

"OHRP does not mandate a specific method of electronic signature. Rather, OHRP permits IRBs to adopt such technologies for use as long as the IRB has considered applicable issues such as how the electronic signature is being created, if the signature can be shown to be legitimate, and if the consent

[29] See http://answers.hhs.gov/ohrp/categories/1566
[30] See http://answers.hhs.gov/ohrp/questions/7249

or permission document can be produced in hard copy for review by the potential subject. One method of allowable electronic signatures in some jurisdictions is the use of a secure system for electronic or digital signature that provides an encrypted identifiable "signature." If properly obtained, an electronic signature can be considered an "original" for the purposes of recordkeeping."

FDA has issued guidance regarding electronic signatures and records at 21 CFR Part 11, with updates in 2007,[31] with specific attention to audit trails and monitoring of research and adverse events. Trace data, logs, time stamps, and electronic data capture can be used.[32]

Q15: Are investigators required to confirm the real identities of the subjects of their Internet research?

Investigators and IRBs should be aware that identity verification is a major issue in Internet research. Absent appropriate verification of a subject's identity, data validity and reliability may be questioned. The need for identity confirmation should take into account:

(a) the importance to the research (i.e., are there critical eligibility criteria? Is there a likelihood of repeat or fraudulent participation, whether for mischief or to collect multiple payments?)

(b) the level of risk to subjects. Low-risk surveys where parental consent could be waived may require only minimal identity verification, perhaps a checkbox. High-risk studies involving the transmission of sensitive information may warrant multiple-factor authentication, such as passwords delivered by mail or telephone, or via an identity verification software or vendor.

(c) There may be a third-party policy or terms of agreement in place that the researcher should consider when considering identity confirmation. For example, Facebook® has a "real-name" only policy, so anonymity is not possible. The norms and expectations of users and venues must be considered.

Online clinical trials, in particular, may include the need for in-person identity verification. Legal jurisdiction should be considered (see Q17). Some IRBs have published suggestions for subject authentication, ranging from sophisticated technical measures such as electronic key exchanges, to less technical personal identification numbers.[33]

~~**Q16: What are the relevant concerns for the knowledge of the local research context, i.e., where research "occurs," during the conduct of online research?**~~

[31] See http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072322.pdf

[32] See for example a level 1 clinical trial use of electronic monitoring: Internet-based technology facilitates clinical outcome data collection and adverse event monitoring, Orthopedics Today, February 2012 (http://www.healio.com/orthopedics/business-of-orthopedics/news/print/orthopedics-today/%7B523CD70A-7C15-4B5D-8E54-923E8BF958EE%7D/Internet-based-technology-facilitates-clinical-outcome-data-collectionand-adverse-event-monitoring)

[33] See the Pennsylvania State University's statement regarding recruitment for Internet research: "Investigators are advised that authentication - that is, proper qualification and/or identification of respondents - is a major challenge in computer- and internet-based research and one that threatens the integrity of research samples and the validity of research results. Researchers are advised to take steps to authenticate participants. For example, investigators can provide each study participant (in person or by U.S. Postal Service mail) with a Personal Identification Number (PIN) to be used for authentication in subsequent computer- and internet- based data collection." (http://www.research.psu.edu/policies/research-protections/irb/irb-guideline-10)

~~In Internet research, in many instances, it may be difficult or even impossible to determine subjects' physical locations. In some cases this information may be irrelevant; in some cases (e.g., research in virtual worlds) the relevant "research context" will be the specific Internet space or venue; and in some cases geophysical location may be important, especially if data or responses may be affected by local culture or local law. *[OLD GUIDANCE HAS BEEN ARCHIVED; WE MIGHT SLOT IN NEW OR EMERGING THINKING HERE.]*~~

Q16: How does legal jurisdiction apply in Internet research?

Jurisdictional authority is complicated by the dispersed nature of Internet subjects and participants. IRBs may assume the jurisdiction of the researcher, not the participants, is controlling. However, in telemedicine, the precedent has held that the jurisdiction of authority is the location of the subjects/patients, consistent with laws regarding the practice and distribution of medicine. This can highlight state and international differences in law and policy. With online clinical trials, for example, state regulations may prevent the enrollment of subjects unless the Investigator is licensed to practice medicine in the state(s) from which subjects are drawn.

Q17: What is minimal risk in Internet research?

102(i)[34]: Minimal risk: The regulatory definition of "minimal risk" predates ~~widespread~~ use of the Internet as a communications and research tool. Many Internet-related risks such as identity theft, other types of electronic fraud or security breaches, online "addictions," and electronic monitoring, stalking, or bullying, can have serious consequences, but most were not part of our daily lives—or indeed even contemplated—when the regulations were first written. It is increasingly appropriate to include the risk of computer-related harms, such as hacking, phishing, breach, lack of appropriate security measures, etc., as among those risks encountered in daily life.

As with any form of human subject research, there runs a continuum of risk in Internet research, and the type of IRB review—~~exempt,~~ expedited or full board—should reflect the level of anticipated risk. Categorization schedules such as the University of North Carolina's Data Security Recommendations[35] or the Harvard Research Data Security Policy[36] can help IRBs determine appropriate protections for data of differing levels of sensitivity. ~~Data~~ use agreements may be necessary supplements to protocols, especially those in cross-agency, cross-institutional, or multi-site studies. In addition, where appropriate under NIH standards, Certificates of Confidentiality offer protection against compelled disclosure.[37]

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[34] 45 CFR 46.102(i): *Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

[35] See http://research.unc.edu/ccm/groups/public/@research/@hre/documents/content/ccm3_035154.pdf

[36] See http://security.harvard.edu/research-data-security-policy

[37] See NIH, "any research project that collects personally identifiable, sensitive information and that has been approved by an IRB operating under either an approved Federal-Wide Assurance issued by the Office of Human Research Protections or the approval of the Food and Drug Administration is eligible for a Certificate. Federal funding is not a prerequisite for an NIH-issued Certificate, but the subject matter of the study must fall within a mission area of the National Institutes of Health, including its Institutes, Centers and the National Library of Medicine." (http://grants.nih.gov/grants/policy/coc/faqs.htm#278)

Investigators and IRBs must consider both risks related to the specific research protocol and risks related to the technologies in use. How should IRBs think about these risks, and how can they accurately be conveyed to subjects—especially when the full extent of risks might not be known even to the investigator? While subjects may be reassured by being told that appropriate precautions will be taken to ensure the security of their data, the exact nature of "appropriate precautions" (in the absence of published guidelines or established standards) can be difficult to determine or to convey in a meaningful way. IRBs that regularly review Internet research should consider including one or more information technology professionals on their rosters, to assist with determinations of actual risk and to advise on implementation of appropriate security measures.

Since research conducted online may not involve real-time communication with participants, misunderstanding or distress may not be evident to the researcher, which can in turn elevate the risk to subjects. IRBs must be aware of these possibilities; some types of Internet research may not be approvable without assurance that immediate contact with a researcher will be available if necessary.

Q18: How may investigators minimize risk of harm when using sensitive online data?

The definition of minimal risk references both the *probability* and the *magnitude* of harm, and investigators and IRBs must consider both dimensions. A risk of significant harm (e.g., identity theft, breach of confidential medical or personal information) that is technically possible, but of small likelihood, may be judged to be minimal if the IRB is satisfied that the investigator's data security procedures are consistent with best-practice recommendations of the institution's IT professionals. Common guidance, or reference to established standards, would be helpful.[38]

Sensitive data include personal health, economic, educational, and/or reputational information, and may be more readily available in online venues than in traditional onground research. IRBs should consider changing sections on consent forms from "Confidentiality" to "Limits to Confidentiality" and should ensure accurate use of terms such as "anonymous" and "confidential."

While the HIPAA standards for protection of data may be extreme for much social/behavioral/educational research, consistent standards for low to minimal risk research should include consideration of how subjects' data will be collected, transmitted to the researcher, and stored. If a third party venue or processing site is involved, their access to and storage of those data should be specified. The consent process should include explanations on how data are maintained, ranging from individually identifiable forms to aggregate forms, and what linking or reidentification measures are possible. If aggregated anonymized data will be made publicly available, investigators and IRBs should consider whether subjects could be (re)identified and how that likelihood could be minimized.

Whenever possible, identifiable data should be encrypted in transit (for most low to minimal risk studies, basic SSL encryption is acceptable) and while at rest (whole disk encryption is readily available). Data should be unlinked from identifiers and IDs destroyed as soon as they are no longer needed. Researchers should consider provisions for remote locking of devices or remote destruction of data in the event of a lost device. When investigators are entrusted with data and devices, they have a responsibility to minimize risk and to honor their obligations to subjects.

[38] See, for example, http://cphs.berkeley.edu/datasecurity.html and http://security.harvard.edu/research-data-security-policy

Both data use and data management plans should reflect investigators' and subjects' responsibilities and rights. In addition to standard elements regarding access, longevity, and ownership of data, plans should identify available resources in the event of harms.

Social media sites, search engines, and virtually all online fora retain log data. A shared knowledge base of appropriate characteristics of venues and tools for IRBs and researchers would be helpful to understand the data life cycle on the most commonly used online research sites and tools.

Q19: What forms of online recruitment are used and what is reviewable by an IRB?

Recruitment tools include Web ads, Twitter streams, blog postings, YouTube videos, and "push" methods, such as email solicitations and texts. Links to online recruitment sites **(e.g., Patients Like Me, Inspire)** may **also** be provided in other media (television, newspaper, classified, public transit posters, Robo-calls, etc.)**.** OHRP considers direct subject recruitment part of informed consent, which is subject to IRB review.

Note that, per FDA guidance, prior IRB review is not necessary for simple listings of clinical trials on websites where the system format limits the provided information to basic descriptive information, including study title, purpose of the study, protocol summary, basic eligibility criteria, study site location(s), and how to contact the study site for further information.[39] Any recruitment plan must receive IRB review and approval prior to initiation if additional information is provided, including description of research risks, potential benefits, incentives (monetary or non-monetary), or where identifiable information is solicited to determine eligibility.

As with **other** forms of research, introducing an investigator into a forum or study site may be appropriate, and the investigator and IRB should review the introduction process as part of the recruitment plan. A moderator, high-ranking member, or other member of status can provide information to the online site community prior to the researcher's entrance.

Q20: How is deception conducted in Internet research?

Occasionally some aspects of a study are not fully disclosed in advance, to avoid **affecting** subjects' responses. Deception in Internet research may be ethically complex; Kraut *et al.* (2003) note greater difficulty in monitoring adverse effects and in provision of adequate debriefing.[40] Internet research

[39] Specifically, refer to clinicaltrials.gov, where study listings that meet the posting criteria of the site need not, in and of themselves, be reviewed and approved by an IRB prior to posting. However,
"Most trials require approval from a human subjects review board. If your study requires approval, you may register your study on ClinicalTrials.gov prior to getting approval if the Overall Recruitment Status of the study is "Not yet recruiting." See Overall Recruitment Status data element on ClinicalTrials.gov .
If a study requires human subjects review board approval, approval must be obtained before the study's Overall Recruitment Status is changed to Recruiting. When board approval is obtained, please update the protocol section of the study record in the Protocol Registration System (PRS) and release the study for processing."
(http://clinicaltrials.gov/ct2/manage-recs/faq#board)

[40] See Kraut, R. *et al.* (2003). Psychological Research Online: Opportunities and Challenges. http://www.apa.org/science/leadership/bsa/internet/internet-report.pdf

provides many opportunities for deception.[41] Researchers can create "fake" or alternative locales to observe behavior or actions; provide limited or erroneous information to see how subjects respond to a given situation;[42] or send "spam" or "phishing" messages to elicit personal data.[43] **Because** informed consent in a deceptive study is necessarily limited, the need for appropriate debriefing following participation must be given special consideration, but difficulties abound. Subjects may choose to leave a venue or locale without reading (or even seeing) the debriefing material; may change email addresses; or may fail to respond to electronic communications. Investigators and IRBs should be aware of these potential challenges when considering appropriate debriefing measures.[44]

[41] See Bachard, K. and Williams, J. (2008). Practical advice for conducting ethical online experiments and questionnaires for United States psychologists. Behav Res Methods. ;40(4):1111-28.

[42] See for example the Virtual Milgram experiment at http://www.plosone.org/article/info:doi%2F10.1371%2Fjournal.pone.0000039

[43] See Finn, P. and Jakobsson, M. (2007). Designing and Conducting Phishing Experiments. IEEE. http://markus-jakobsson.com/papers/jakobsson-ieeets07.pdf

[44] See for example, University of Massachusetts: "Some research requires a debriefing after participants have completed an online survey. Online debriefing forms should be similar to the debriefing process done during in-lab experiments. The debriefing page should come immediately after the last question on the survey. Participants should be thanked for participation and more information as to the purpose of the study should be provided. Also, researchers contact information and information about other resources (IRB info, Health Services, Local Resources) should be provided and participants should be reminded to print a copy of the debriefing form for their records. Participants should also be given the option to withdraw their data at this point (now that they have been fully informed as to the intent and purpose of the study). If they agree to have their data used for the study then they should have an "I Agree" button to click and submit their data online. If they do not agree to have their data used in the study they should have an "I Do Not Agree" button to click so that their data is not submitted and collected online. Please check with the online survey program you are using to ensure that these capabilities are allowed." (http://www.umass.edu/research/online-surveysurvey-research-guidance)

Secretary's Advisory Committee on Human Research Protections
October 9-10, 2012
Washington, D.C.

Certification of the Summary of Minutes

I hereby certify that, to the best of my knowledge, the foregoing summary of minutes is accurate and complete.

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Barbara Bierer, M.D., Chair Date